92-1289

No. -

Supreme Court, U.S.
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In the Supreme Court of the United States

OCTOBER TERM, 1992

JOSE M. OTERO, PRO SE,
PETITIONER,

v.

INTERNATIONAL GENERAL ELECTRIC CO., ET AL.,
RESPONDENTS.

APPENDIX TO PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

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APPENDIX A

[NOT FOR PUBLICATION]

United States Court of Appeals
For the First Circuit

No. 91-1987

JOSE OTERO LABORDE,

PLAINTIFF, APPELLANT,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,

DEFENDANTS, APPELLEES.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF PUERTO RICO
[HON. JOSE ANTONIO FUSTE, *U.S. District Judge*]

Before

BREYER, *Chief Judge*,
CAMPBELL, *Senior Circuit Judge*,
and CYR, *Circuit Judge*.

Jose M. Otero Laborde on brief pro se.
Francisco Agrait-Oliveras on brief for co-defendant and co-appellee General Electric Company.
Rafael Escalera-Rodriguez and *Lasa, Escalera & Reichard* on brief for defendant-appellee Mallinckrodt Corporation.

June 29, 1992

Per Curiam. On February 26, 1987, plaintiff-appellant Jose Otero Laborde, along with several relatives, filed through counsel a diversity complaint in the District of Puerto Rico

against defendants-appellees International General Electric Co. ("GE") and Mallinckrodt, Inc. ("Mallinckrodt"). The complaint alleged that Ruben Otero Laborde, plaintiffs' relative, died from anaphylactic and respiratory arrest suffered while undergoing a CT scanning test at the CT Scan and Radiology Center in Hato Rey, Puerto Rico. Under products liability theories, relief was sought against GE as the manufacturer of the test machine, and against Mallinckrodt as the manufacturer of Conray 60, the contrast medium injected into the deceased as part of the medical procedure. The main theory of recovery was that both GE and Mallinckrodt had failed to adequately warn of risks associated with use of their products.

A jury trial commenced on plaintiffs' claim on October 11, 1988. On the third day of trial, the district court granted GE's motion for a directed verdict on the ground that plaintiffs' evidence against GE was insufficient to support recovery. Mallinckrodt's motion for a directed verdict was denied. At the conclusion of the trial, plaintiffs and Mallinckrodt informed the court that they had agreed to a settlement stipulation. Accordingly, the jury never deliberated. The district court entered judgment for GE and also entered judgment dismissing the complaint against Mallinckrodt pursuant to the parties' stipulation. Plaintiffs filed a notice of appeal to this court, but on December 12, 1988, the district court granted plaintiffs' motion to withdraw the notice of appeal.

On July 18, 1991, over two and one-half years later, plaintiff-appellant Jose Otero Laborde (hereinafter "Otero"), proceeding *pro se* purportedly on behalf of himself and the other plaintiffs, filed a motion to reopen the case on the ground that the district court's judgment was procured by fraud committed through a conspiracy between GE and Mallinckrodt. The district court summarily denied Otero's motion. Otero appeals. We affirm.

The district court's denial of Otero's motion was proper for several reasons. First, Otero filed the motion *pro se* on behalf

of himself and the other plaintiffs. Otero has not denied appellees' assertions that he is not an attorney and has not been admitted to the bar of the District Court for the District of Puerto Rico or of this court. Although Otero may represent himself *pro se*, he cannot represent other plaintiffs. Thus, Otero's motion was properly denied insofar as it was filed on behalf of any plaintiff besides Otero himself.

Second, although Otero styled his motion as a "motion to reopen case" on grounds of fraud, the motion is, in substance, clearly filed under Fed.R.Civ.P. 60(b)(3). Rule 60(b) provides: "On motion and upon such terms as are just, the court may relieve a party or a party's legal representative from a final judgment, order, or proceeding for the following reasons: . . . (3) fraud (whether heretofore denominated intrinsic or extrinsic), misrepresentation, or other misconduct of an adverse party." Rule 60(b)(3) describes precisely the kind of basis for relief from judgment that Otero's motion alleged.

Rule 60(b) goes on to provide, "The motion shall be made within a reasonable time, and for reasons (1), (2), and (3) not more than one year after the judgment, order, or proceeding was entered or taken." We have held that untimeliness under this provision is "an absolute bar to relief from the judgment." *United States* v. *Marin*, 720 F.2d 229, 231 (1st Cir. 1983). In this case, Otero's July 18, 1991 motion to reopen — a Rule 60(b)(3) motion — was filed well over two years after the district court's October 18, 1988 judgment. Accordingly, Otero's motion was properly denied as untimely.

Finally, if more were needed, we would affirm the denial of Otero's motion on its merits. We would review the denial only for abuse of discretion. *United States* v. *Boch Oldsmobile, Inc.*, 909 F.2d 657, 660 (1st Cir. 1990); *Rodriguez-Antuna* v. *Chase Manhattan Bank Corp.*, 871 F.2d 1, 3 (1st Cir. 1989).

Otero claims that medical expert witnesses at trial gave testimony that was inconsistent with a number of prior medical publications that the witnesses themselves had written. The

publications, according to Otero, are far more favorable to Otero's position than the witnesses' testimony at trial. Otero characterizes the alleged discrepancy as fraudulent and asserts that it was the result of a conspiracy by GE and Mallinckrodt to defraud the court.

None of these witnesses were called by GE. Otero provides no factual substantiation whatsoever for his bald assertion that GE somehow improperly influenced their testimony.

All of the witnesses, instead, were Mallinckrodt witnesses. Otero reached a settlement agreement with Mallinckrodt. Thus, Otero's claims against Mallinckrodt were dismissed pursuant to the settlement stipulation, not pursuant to any jury or court determination that would have been influenced by the allegedly fraudulent testimony.

In any event, it is not at all clear from a review of the record, and of the medical publications supplied by Otero, that any genuine, thoroughgoing inconsistency existed. The district court would have acted well within its discretion to conclude that Otero's filing did not point to the kind of glaring contradictions that might conceivably suggest possible misconduct.

Having reviewed Otero's motion, we would also rule that the district court did not abuse its discretion in rejecting any other grounds for relief from judgment that Otero's motion could be read to raise.

In view of Otero's *pro se* status, GE's request that attorneys' fees be assessed against him is *denied*.

Otero's motion filed in this court to supplement the record is *denied*. The clerk is directed to return to Otero the materials he attached to his motion to supplement the record.

The district court's denial of Otero's Fed.R.Civ.P. 60(b) motion is *affirmed*.

United States Court of Appeals
For the First Circuit

No. 91-1987

JOSE OTERO LABORDE,
PLAINTIFF, APPELLANT,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
DEFENDANTS, APPELLEES.

JUDGMENT

Entered: June 29, 1992

This cause came on to be submitted on the briefs and the original record on appeal from the United States District Court for the District of Puerto Rico.

Upon consideration whereof, It is now here ordered adjudged and decreed as follows: The district court's denial of Otero's Fed.R.Civ.P. 60(b) motion is affirmed.

By the Court:

FRANCIS P. SCIGLIANO, Clerk.

By DANIEL F. LOUGHRY
Chief Deputy Clerk.

[cc: Messrs: Otero Laborde, Agrait-Oliveras and Escalera-Rodriguez]

United States Court of Appeals
For the First Circuit

No. 91-1987

JOSE OTERO LABORDE,
PLAINTIFF, APPELLANT,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
DEFENDANTS, APPELLEES.

Before
BREYER, *Chief Judge*,
CAMPBELL, *Senior Circuit Judge*,
and CYR, *Circuit Judge*.

ORDER OF COURT

Entered September 2, 1992

Plaintiff-appellant Jose Otero Laborde's motions to supplement his petition for rehearing are granted insofar as they seek to add supplementary legal argument. These motions are denied insofar as they seek to add papers, documents, or other evidentiary materials. The clerk is directed to return these materials to Otero.

Otero's motion for an enlargement of time to make a further submission in support of his petition for rehearing is *denied*.

Otero's petition for rehearing is *denied*.

By the Court:

FRANCIS P. SCIGLIANO, Clerk

By: DANIEL F. LOUGHRY
Chief Deputy Clerk

[cc: Messrs: Otero Laborde, Agrait Oliveras,
Escalera Rodriguez and Humberto Vargas]

CLERK'S OFFICE

United States Court of Appeals
For the First Circuit

No. 91-1987

JOSE OTERO LABORDE,
PLAINTIFF, APPELLANT,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
DEFENDANTS, APPELLEES.

September 10, 1992

Mandate herein issued today.

FRANCIS P. SCIGLIANO, Clerk.

United States Court of Appeals
For the First Circuit

No. 91-1987

JOSE OTERO LABORDE,
PLAINTIFF, APPELLANT,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
DEFENDANTS, APPELLEES.

ORDER OF COURT

Entered October 2, 1992

Appellant's motion to stay mandate, treated as a motion to recall mandate, is *denied*.

By the Court:

FRANCIS P. SCIGLIANO
Clerk.

[cc: Messrs: Otero Laborde, Agrait Oliveras, Escalera Rodriguez and Humberto Vargas]

APPENDIX B

In the Supreme Court of the United States

No. A-377

JOSE OTERO LABORDE,
PETITIONER,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
RESPONDENT.

ORDER

UPON CONSIDERATION of the application of counsel for the petitioner,

IT IS ORDERED that the time for filing a petition for a writ of certiorari in the above-entitled case, be and the same is hereby, extended to and including 30 January, 1993.

/s/ DAVID H. SOUTER
Associate Justice of the Supreme Court of the United States

Dated this 9th
day of November, 1992.

APPENDIX C

United States District Court
For the District of Puerto Rico

JUDGMENT

Judgment is entered dismissing the complaint against G.E., and also Judgment entered dismissing complaint against Mallinckrodt, Inc. with prejudice, pursuant to the stipulation of the parties.

October 18, 1988

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF PUERTO RICO

Civil Case No. 87-0278
October 11, 1988
San Juan, Puerto Rico
Before The Honorable
Jose Antonio Fuste

JOSE OTERO LABORDE, ET AL.,
PLAINTIFFS,

v.

INTERNATIONAL GENERAL ELECTRIC COMPANY, ET AL.,
DEFENDANTS.

JURY TRIAL PROCEEDINGS

Appearances:

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Hato Rey, Puerto Rico 00919

* * * **VOLUME II** * * *

[339] developed for the record by Mr. Agrait, accept the argument he made on the, on Article 1443 of the Civil Code, which I don't think is of application to this case.

There is nothing in this record that suggests, by a preponderance of the evidence, not even a scintilla of evidence, taking all the evidence as proof positive that General Electric was negligent in this case in any form or fashion.

As a matter of fact, the testimony by Dr. Ramon Franco points the finger to the radiologist. It is as simple as that and, perhaps, to Mallinckrodt; but there is nothing against G.E. in this case. I just don't think, nobody, unless you really want to find absolute liability, because you manufactured a C.T. Scan Machine, that would be the only possibility that you could really find them liable here. If you are going to hit them with a judgment simply because they manufactured the machine.

There is nothing in this record that can sustain a judgment against G.E.

At least I don't see it. And, therefore, a judgment will be entered dismissing the complaint against G.E. Directed verdict will be entered as to that. I will enter that today.

Anything else?

MR. ESCALERA: Yes, your Honor, Mallinckrodt — [340] Excuse me, are you addressing —

THE COURT: No, I am asking anything else from anybody.

MR. AGRAIT: May we ask permission to leave?

THE COURT: If you want to, yes. Your case is over.

MR. ESCALERA: Your Honor, Mallinckrodt Corporation respectfully requests permission to present its motion for directed verdict.

THE COURT: I don't think you are going to be that lucky, but I will hear you. Make a record but I assure you now I am going to deny you.

MR. ESCALERA: Your Honor, we feel that as to Mallinckrodt Corporation, this case is basically a case on causation.

THE COURT: If it is on causation, it is a jury fact —

MR. ESCALERA: It is also, your Honor, a case on whether there has been evidence of the existence of a duty to warn in this particular case.

The evidence has shown, your Honor, that the insert contains warnings about the possibility of a lethal reaction in any case.

It also warns the radiologist that he has to be prepared, always, no matter whether the patient is a high [341] risk patient or not.

The evidence has also established that this person had a particularly, very well known risk condition, which is asthma.

The record also establishes that the only reason why this patient was not premedicated and that special precautions were not taken, is the fact that the radiologist did not know about the risk conditions that were present in this particular patient, your Honor.

Dr. Lazaga has testified that he knew of the risk, both, presented by both asthma and urticaria pigmentosa.

It doesn't matter whether he has knowledge of the risk by urticaria pigmentosa. Comes from the fact that he mistakenly, by February of 1986, associated the urticaria pigmentosa with an allergy.

He has testified, your Honor, that by reading allergies back in February of 1986 he knew that he was dealing, also, with urticaria pigmentosa.

In that case it is impossible that the failure to warn had a causal relationship with the death of this person.

Additionally, your Honor, plaintiff's own expert testified that this patient had 96 percent opportunity to survive and that he didn't because he wasn't resuscitated properly.

It is plaintiff's own expert who has —

[342] THE COURT: You just, you just are doing now what I tried to convince Mr. Lopez not to do before. You have to see the broad picture.

I am not saying that plaintiff's case is the best case against Mallinckrodt. All I am saying is there is a jury question here. This case should go to the jury as to Mallinckrodt. Same way that it will eventually go to judgment on the doctor. In local court.

Because what happened here, really, from what I heard, is that, I am going to borrow from Laborde's own testimony, his brother was caught in the middle of these things and he was the victim of circumstances. That is what happened here.

It is unbelievable that a first class hospital like Auxilio Mutuo would refer a patient without a record to a free standing facility where, obviously, there were not necessarily facilities needed to deal with a situation like this. A radiologist relies on a nurse, doesn't even ask a question from the person, and in the best of faith, injects this thing and kills him.

That is what happened here. It is a very bad case against this physician, let me tell you, and against the hospital; but they are not here before me. Terrible case.

But I think that as to Mallinckrodt the case will have to go to the jury.

[343] MR. ESCALERA: The problem is —

THE COURT: The problem is the case is going to the jury. Simple as that. Motion denied. There is no way this case can go under Rule 50, no way.

MR. ESCALERA: Okay, your Honor.

THE COURT: Very well, we will bring the jury back.

Let me tell you more. I think in my own mind this was going to happen, with or without the insert, but this is a question, any way.

MR. ESCALERA: Excuse me, your Honor, with or without.

THE COURT: I am saying with or without any insert. The way this happened to happen. It is a fact. Mr. Otero's position is correct. That is a fact. That is what happened.

I only hope nobody else gets caught in that situation. It is bad news. It is not a matter of inserts or a matter of — it is a matter of mass production without taking enough care about a human life. That is all. That is what happened.

The reason we don't have the physician here is because there is no jurisdiction. And you split your case up in two pieces, I don't know whether that was a correct decision or not. That is not my business.

Mr. Lopez, the truth of the matter is, the strongest case is against the physician, that is for sure.

* * *

[424] THE COURT: Those will now become defendant's exhibits F and G.

MR. ESCALERA: Which one which?

THE COURT: Number one is F, No. 4 is G. Let the deposition exhibit label stand there so we will know what it is. Put it on the side. What else?

MR. ESCALERA: That is it in this case, your Honor.

THE COURT: So you are resting, too.

MR. ESCALERA: Yes.

THE COURT: No additional evidence.

MR. ESCALERA: No, your Honor.

THE COURT: Very well. At this time we are going to do following: We are going to take half hour recess for the juries' behalf. For the lawyers 15 minutes. Because I will take up some matters with you in 15 minutes, Okay?

MR. ESCALERA: Yes.

*** RECESS ***

THE COURT: Counsel, any additional request before we conclude this stage of the case?

MR. LOPEZ: Can we approach the bench, your Honor?

THE COURT: Please.

*** BENCH CONFERENCE OFF THE RECORD ***

THE COURT: The parties have decided to dispose of this case through extra judicial means. Therefore, at this time, the plaintiffs are entering a voluntarily dismissal [425] with prejudice in this case. And a judgment to that effect will be entered accordingly.

There are some private agreements between the parties that will be disposed of within the next 20 days. The court is aware of them.

MR. LOPEZ: Your Honor, I would like to state, for the record, on behalf of my clients, our appreciation of a very good trial you have given us.

THE COURT: Well, I have tried. I tell you one thing, I can, I have to explain to the jury what happened, I will try my best without giving them the details because they have been here a week. Least I can do.

I see the point of both of you. Nobody likes to see a 34 years old man die the way this man died. That is not, that is not something easy to accept.

However, you know, medical practice these days is this way. I think that what Mr. Laborde said, the point is true, trying to explain his feelings of the case.

The problem is that this person was caught in the fast lane of this firsthañd facility, and those things may happen under those circumstances.

He ended up in a bad posture at a given point in time. Odds were against him at that moment. And your strong case is definitely the hospital referred him to an outside facility with

that paper slip that says nothing. Medical [426] record developed by a nurse or, God knows who. And no inner action between physician and a patient.

The patient not being a physician either, bunch of things happen. Bad news, and then on top of it, reaction plus failure to treat adequately. That is what happened here.

I know of a person who died from taking a penicillin capsule, one. Give you any idea, you can buy them on the, over the counter in a drugstore. Those things happen. That is the way it is.

The greatest danger is living. If you are living you are in the greatest danger possible. I think you have done the right thing. I think you have done the right thing because you are at least getting something.

You have gained some monetary benefit. You have given them the psychological reward of winning, up to a certain point, being redressed in that sense.

And on top of that, you know Mallinckrodt had to do something which is very practical. Multi million dollar operation cannot put the name of a product in jeopardy because of a $100,000. As simple as that.

They are commercial approaches to this thing that are not necessarily legal.

MR. LOPEZ: I also believe, your Honor, that as a result of this case, people like Mr. McClennen, they are [427] thinking about this. As you just heard from the —

THE COURT: I tell you one thing, all the doctors that are involved in this are better doctors. If there is anything else to say, all I can say is that, perhaps, these things sometimes have to happen so that medicine gets to a better stage. Tragically, but that is the way it is.

MR. ESCALERA: Yes.

THE COURT: You all hope and pray you never end up in that predicament.

MR. ESCALERA: Your Honor, we want to join Brother Counsel in the recommendation of the work you have done.

It was my first experience with you. And it was an excellent experience. I have learned a lot from you.

THE COURT: Try a lot.

Let's call the jury in and try to explain it to them so they won't think the case is now over. You know. They have done nothing.

*** JURY WAS PUT IN THE JURY BOX ***

Members of the jury, the parties came to me and we discussed some of the potential implications that are involved in this case, and after they consulted with their respective clients, they agreed that, perhaps, the best course of action was to stop the case right here, dispose of it by just dismissing it. And they will, of course, continue with the case that is in the local court. The case against [428] the hospital, against the physicians.

So the case is going to be concluded. You will not have to do anything else, and I will not have to do anything else at this time.

Don't think, don't think that you have wasted that many days being here with us and me, of course, being here with you and with them.

You should, I should tell you a little bit of the history of this case, I think, so you should know about it now that the case is over.

I learned after I started this case that there was a prior case right here in this Court whereby the widow of the gentleman who died, and the girl, sued, and that was disposed of. I did not know that. I was not the judge who handled that. That was against the physicians.

Then, of course, lawyers decided to sue General Electric, and Mallinckrodt and that is the case we have here. We have here, up until now. Plus a similar case like the one originally instituted here in local court. Because of jurisdiction problems, more than anything else.

The first one was concluded and the second one, third one will be concluded, perhaps, this year in local court.

What happened with General Electric was that I dismissed the case. In my own mind I thought there was no [429] way that G.E. could be responsible because the only thing they did was make the machine. And that is what happened.

And now this case is concluded for other reasons, and as I said, they are going to continue with the case in local court.

I think that all of us have a lot to learn from things like this. And that is the important thing.

First of all, it is not pleasant, as I discussed with the lawyers and the lawyers here, it is not pleasant to see a 34 year old man in a situation of Mr. Laborde, go to a hospital and be referred for a C.T. Scan with a little piece of paper, nothing else, and then he goes there and before much time he lapses and he is given this media, contrast media, and all of a sudden he dies.

You will make your own conclusions; you are entitled to deliberate while you are going home. Seems to me it is quite obvious what happened.

Seems to me that now days medicine, the art of medicine is very complicated. And, perhaps, what Mr. Jose Otero said when he testified was true. You remember when he said something to this effect: That his brother was caught in the middle of this maze, this thing that goes on in medicine these days.

On the one hand we have advanced a lot. And there are some economical factors involved. When people are making [430] money, some people are thinking in terms of patients, too many things happened. He was caught in the middle of this and it happened.

Seems to me that, seems to me that if it happened, it is only one benefit and the benefit is that the doctors were involved, who were involved, will be involved, will be, perhaps, more aware of a lot of things.

And that alone is a benefit. It seems to me that unless people go through things medicine doesn't seem to advance. That is a tragedy, but that is the way it is.

And I think that they have done the right thing. It is always good when the parties look at their case and look at their respective postures and they think that they better keep it under control and not in the control of others.

What they have done is a good thing, proper thing to do. So I urged them to look at this possibility and they did, and I think they have done the right thing. And these lawyers have done their job on both sides, three sides, and all of us should feel that something was accomplished, even though there was no burden.

So at this time I am going to excuse you from further participating in this case, and as I said before, I want to thank you on behalf of the judges of the Court for your participation. Three of you are serving your last day. [431] Mr. Lopez, today is your last day, and Mr. Marrero, your last day, and Felix Perez, your last day, also.

Thank you on behalf of the judges of the Court, once again, for those of you who have to come back and the three of you who are leaving us, thank you very much for giving us a hand in doing these things.

Remember what I told you at the beginning, it is very difficult, if not impossible for the judges to give any kind of assistance to the parties unless people like you are willing to give your interest and attention to this kind of dispute. It is difficult if we don't do it this way.

The others will have to come back on October 31 at 8:00 o'clock in the morning for a trial before some judge. I don't know whether it is me or somebody else, but just in case, that is the date. October 31.

Another thing to learn is this: Seems to me that each person, aside from, it may be in the hands of the best physician ever, but each person has a responsibility to be very much aware of his own particular conditions and his own things. It is, you have to get, to really develop a lot of knowledge, as a citizen, as a person who is subject to medical treatment, as to what may happen and what may not happen to you.

Seems to me that that is very important, that people get to know more about things that they are about to [432] go when they seek physicians. It is very important.

Because as I said before, it is very difficult. If everybody is not really concerned, the prime thing, which is health. The rest is secondary, should be secondary.

Well, with those comments I will let you go. I want to thank the parties and the lawyers for their intervention.

And that will be the end of the case. Thank you very much. You can leave now.

*** TRIAL PROCEEDINGS WERE CONCLUDED ***

APPENDIX D

Japanese Journal of Allergology

— "Allergic Activation of Most Cells"

by Dr. Charles W. Parker

JAPANESE SOCIETY OF ALLERGOLOGY

Charles W. Parker

* * *

[307] *Mast cell and basophil mediators*

Mediators which may contribute to IgE mediated responses depending on the level of allergic sensitivity, location of response and stage of the reaction include histamine, leukotrienes, kinins, PAF, neuropeptides and prostaglandins (Table 2). In addition to IgE mediated mechanisms there are a variety of processes which may lead to secretion of mediators by mast cells and basophils. These include exposure to hyperosmolar solutions (such as the polyiodinated contrast media used in radiologic procedures), the anaphylotoxins (8000-2000 molecular weight fragments of C3, C4 and C5 which release histamine), stimulators or modulators of secretion of a hormonal or cell regulatory nature such as acetylcholine, adenosine and the various neurosecretory hormones, proteolytic enzymes, various drugs, polycations and an ill-defined group of products produced by lymphocytes and macrophages which may directly affect secretion by these cells. Finally there are the hormones such as IL3 which not only stimulate mast cell replication but may also induce enzyme systems involved in histamine and other mediator synthesis. Since non-IgE stimuli can produce secretion, the possibility must be considered that disease states associated with allergy-like symptoms may involve these or unknown stimuli of secretion. Other possibilities include altered numbers of mast cells, or mast cells which are not subject to the usual regulatory controls and spontaneously secrete mediators in the absence of the usual types of stimuli. In systemic mastocytosis, symptoms such as hypotension and urticaria, probably due primarily to PGD_7 release may be prominent and even life-threatening. What is even more interesting are patients with similar clinical syndromes and demonstrable PGD_7 and histamine release who have

Table 2

Possible allergic mediators and modulations from mast cells and basophils

Histamine
Leukotrienes A,B,C,D,E
PAF
Kinins
Prostaglandins, especially PGD_7
Neuropeptides
Serotonin
ATP
Proteases
ILLEGIBLE

[308] no obvious clinical stigmata of mastocytosis such as urticaria pigmentosa and by skin biopsy may or may not lack the usual pathologic criteria or mastocytosis. It is possible that there are indeed increased numbers of mast cells elsewhere in the body in these individuals. Alternatively, the mast cells may be normal number but unusually active in secreting even though IgE mediated allergy is absent or minimal. There is a real possibility that diseases such as idiopathic urticaria and idiopathic asthma may represent diseases or altered mast cell (or less likely basophil) secretion. While limited studies have been made of levels of histamine or its metabolites in these diseases in sputum, urine and blood other markers of mast cell secretion should be studied and more extensive analyses of mast cell numbers and mediator levels in biopsy tissues would be desirable. As blocking agents for mediators such as the leukotrienes become available, they may help to clarify the role of mast cell products in these conditions. When more specific assays become available the possible role of products of lymphocyte or monocyte metabolism which may affect mast cell secretion should also be studied. Factors responsible for the nonspecific increase in bronchial reactivity in allergic and nonallergic individuals with asthma also require further study.

While the emphasis has been and should continue to be on soluble mediators, secretion by mast cells and basophils may involve extrusion of the granules from the cells. Based on the work of Kaliner and others it appears that the residue of the granule left after substances such as histamine have been solubilized may itself contribute to an ongoing hypersensitivity response. This would help the response to persist long after mediators such as histamine have been dissipated.

* * *

Parker's Testimony, List of Medical Reference Literature. (c)

[23] Q. Why is it a difficult thing to quantify?

A. Because there are many tissues which contains mast cells and you have to do an awful lot of sectioning and counting in order to arrive at an estimate.

Q. And — doctor, we are talking about an increase number of mast cells, are mast cells something that are present in — normally?

A. Mast cells are normally present and they're present in considerable quantities and they're present in many organs through the body, they are present in the bone marrow. You can suspect a diagnosis of systemic mastocytosis on the basis of increase of numbers of mast cells in the bone marrow, but it's hard to make the diagnosis for sure because increase numbers of mast cells have been describe in the bone marrow in a variety of conditions and the deposition of mast cells in different tissues tends to be rather spotty, the distribution is uneven, so unless there is a careful examination of the tissue it would be easy to underestimate or overestimate the number of mast cells that are there.

Q. What are the normal number of mast cells?

A. Well, it's hard to arrive at precise criteria that people agree on, as to exactly what the number of — normal number of mast cells is. And in fact in its monograph on mastocytosis, Seghers published in 1967, which is an extensive . . .

* * *

List of Medical Reference Literature, Parker (d)

[44] point against the mast cells in the skin, having reacted either. But, in any case, it still would be speculation as to what caused his reaction because he has another, much better, established risk factor, and —

Q. Which was?

A. — which was the asthma, which he was known to have had for a long time.

Q. And what do you mean by "well established" risk factor?

A. Well, all of the studies that have been performed, that have been thorough and have looked at diseases that predispose to serious reactions in individuals receiving contrast media, have indicated that a history of asthma, is a very significant risk factor, increasing in the risk of a reaction. In the range of three to five, fall over that, in that the otherwise unselected population.

Q. Which of those studies indicate that urticaria pigmentosa is a risk factor?

A. There is no evidence, as far as I have been able to find, that urticaria pigmentosa is a risk factor for serious dye reactions.

Q. Have you seen it mentioned in any literature, as a risk factor?

A. No. I have not.

List of Medical Reference Literature, Parker (e)

[45] Q. Doctor, you also said before, that in addition to mast cells, basophils also are capable of releasing histamine is there an increased number of basophils in patients with urticaria pigmentosa?

A. No. They — the basophil content of the blood is normal. There are no alterations that are known. That's a different type of cell with a different linage than the mast cell; and basophils are not altered in mastocytosis.

Q. In which of the two basophils or mastocytosis receive more direct contact with the dye?

A. The basophils are in the bloodstream; some of them, of course, are other places; but one of their main locations is in the bloodstream, where they come in direct contact with the

dye, as the dye is injected. So, they are very much at risk, in terms of being stimulated by the dye; and they would release histamine, and they could explain where increases in histamine have been observed, where the histamine is coming from and in fact, they would be a considerably better explanation than mast cells in the tissue, would be.

Q. Doctor, I am going to ask you now, to state briefly, for us, what is your conclusion regarding the relationship between urticaria pigmentosa and an increased risk of a dye reaction.

A. There is no evidence that urticaria pigmentosa . . .

List of Medical Reference Literature, Parker (f)

[46] predisposes to dye reactions.

Q. And in your opinion; does it?

A. I haven't been able to find anything that said that — I think it is likely that the dye doesn't get into the skin, in a high enough concentration and it isn't good enough release here of histamine, to represent a substantial risk.

You know, if you said, could I say, would it never happen? No. I could not say that.

Q. Okay.

What does this evidence that you have just related to us, tell you about the suggestion, that a contrast material injection cause a histamine release reaction in Mr. Otero; the specific patient of this case?

A. Again, I find no evidence that patients are at risk, based on what is in the literature and I find no evidence based on the examination at the time of his reaction or subsequently, that release of histamine had — release of mediators had occurred in his skin, in association with the reaction, and if that hadn't occurred in his skin, we don't know of any mast cells that are demonstrated elsewhere in the body, to service the source of the histamine —

Q. Umhum.

A. — and the skin itself, should have reacted and should have reacted quite massively, I would think.

* * *

List of Medical Reference Articles, Parker (k)

[62] ultimately, it's — if we can arrive at a completely effective prevention protocol, that's exactly what should be done.

Q. Okay. But that's not the reality —

A. That's not the reality of right now. I mean, we are still trying to find out and make sure that we have effective prevention programs and I think the evidence that's emerging is, that we do, but they could be better.

Q. Okay.

Doctor, in your opinion and according to the studies that you have personally performed to the medical literature that you have examined and the evidence that you have come in contact with, throughout your years of professional experience; what should — what is your conclusion regarding what should have been done by Mallinckrodt with regards to the inclusion of a warning of urticaria pigmentosa as a risk factor in the inject of contrast material, back in February of 1986?

A. Well, I don't think they should have a warning for something that hasn't been shown to be a risk. I suppose sometime, there may be a serious reaction, in it, in urticaria pigmentosa patient but the package inserts that go with these dyes are already quite long and complex and Mallinckrodt and the other companies that marketed these dyes, are required by law, to report any serious reactions, including, of course, the fatal reactions that are reported to them. They . . .

* * *

Medical Reference Literature, Parker (g)

[81] me uneasy in terms of a serious dye reaction, which is what you are worried about.

Q. And how about in the case of a person with mastocytosis?

A. Well, this patient did not have mastocytosis —

Q. That is not the question.

A. — a systematic mastocytosis.

Q. Doctor, that is something for the jury to conclude, upon evaluating opposing testimonies of two experts. That is not my question. My question is, whether a patient with the condition of mastocytosis would have a higher risk of having an adverse reaction?

A. The evidence from the literature from reported dye reactions in a series of patients with serious adverse reactions, which is what we are concerned with, here does not show either condition, as a predisposing condition to more severe reactions.

Q. Now, using Mallinckrodt's insert —

A. This is not based just on Mallinckrodt's word. It's based on large-scale studies in reviews, taking data from . . .

* * *

Reference Medical Literature, Parker (h)

[99] people who had the condition of urticaria pigmentosa, by injecting them with such a high risk product like the hyperosmolar —

MR. ESCALERA:

But Brother counsel is insisting in arguing.

MR. LOPEZ:

Conray-60. That is the question, doctor.

MR. ESCALERA:

Brother counsel is still arguing. There is — that is — there is no question being posed. If Brother counsel wants to pose a question, please go ahead.

MR. LOPEZ:

The record is clear. We insist on our question and the judge will decide. We proceed.

MR. ESCALERA:

What is the question?

BY MR. LOPEZ:

Q. Doctor, is there anything in the medical literature that expressly states, that a radiologist can inject radio contrast material, Conray-60, to a patient with urticaria ...

Medical Reference Literature, Parker (i)

[100] pigmentosa, mastocytosis, at no higher risk than a patient who does not have urticaria pigmentosa mastocytosis.

A. Not that I have seen.

Q. If there is nothing in the medical literature, that permits the injection of radio contrast material on the patients who have the condition of urticaria pigmentosa mastocytosis; how can it be of general medical knowledge, that these patients can be injected without increasing risk of anaphylactoid reaction to the patient?

A. Well, I think my response to that is, that normally, the decision that a condition represents a risk, as far as the dye injection is concerned, is based on the experience that the use of the dye in that disease or condition, is associated with reactions in apparently higher, incidents than when — with — would otherwise, be expected.

The company, I don't think is in a position to judge what diseases are likely to represent risks and which ones are not; and in any case, the dyes have been in use for more than fifty years and certainly, have been used in patients with every conceivable disease, by now, and while it's possible, that a careful study of patients with urticaria pigmentosa, in relation to dye injections, would show that there is some risk; as far as I am aware, and as — I assume, as far as Mallinckrodt is aware, that study does not exist at this ...

Reference Medical Literature, Parker (j)

[101] particular point in time. So, —

MR. LOPEZ:

Mr. Lasa — Mr. Escalera, I'm sorry; already stated that you are not, at this moment, speaking for Mallinckrodt.

THE DEPONENT:

All right.

BY MR. LOPEZ:

Q. Now doctor, let's go back to the statistics.

Would you agree that eight percent of the persons injected with radio contrast material, suffer adverse reactions?

A. Yeah. It figures very — anywhere from five to eight percent. Occasionally a little higher. Occasionally, a little lower but those are reasonable numbers, I think.

Q. And those eight percent suffer between mild reactions, moderate reactions or serious reactions; is that correct?

A. Yes.

Q. What percentage of the reactions are mild?

A. Well, the great — the vast majority are mild.

Q. What percentage?

A. Well, I would say, all but about — the serious ones are about point one percent. At least, according to some estimates.

STATE OF THE ART

Bruce L. McClennan, MD

Low-Osmolality Contrast Media: Premises and Promises

* * *

Classification

While not all radiologists agree on the categories of adverse side effects, most classifications are based on Ansell and Shehadi's grading system (Table 2) (43, 44, 50). While the overwhelming majority of adverse side effects are mild to moderate and nonfatal, in Shehadi and Toniolo's large series where the overall incidence was calculated to be 4.7% for unselected patients, mild or minor reactions occurred in up to 3.3%. Moderate reactions occurred 1%-2% of the time (50). Additional conclusions from this same report show the incidence of intraarterial contrast media reactions was only 2.3% overall. Severe, life-threatening, or fatal consequences of HOCM injections occurred about .009% of the time, according to the study with the highest estimate of death following intravenous contrast material administration — 1/10,931 (50). This translates to over 550 deaths per year from intravenous contrast material-assisted imaging procedures in the United States (4). Focusing only on urography and CT studies, because these procedures usually utilize the largest doses of contrast material, the incidence of deaths ranges from 1/40,000 (.003%) to 1/66,502 (54). These numbers take on additional significance when the aspect of dose is considered. Fewer contrast material reactions have been reported with doses less than 20 g of iodine (43, 44). For mild or moderate reactions, there does not appear to be any relationship to dose, but most severe reactions occurred at doses greater than 20 g of iodine (43, 44). Such data further refine the focus on the chemotoxic and adverse physicochemical properties (e.g.,

osmolality) of contrast material as important factors in severe or life-threatening reactions.

Initial data based on the use of LOCM for intravenous procedures show that the incidence of contrast material reactions has been reduced, to less than half the number associated with HOCM (e.g., 2.1% overall incidence using iohexol) (55). Estimates of deaths from manufacturers' statistics approximate 1/250,000 or more (.0004%). Most fatalities associated with the intravascular use of the new LOCM appear to be in very ill or "allergic patients or not clearly related to the LOCM itself (Mallinckrodt), personal communication, October 1986). The major problems with data obtained from manufacturers or even from the Federal Drug Administration (FDA) is that when one considers the data in terms of a numerator-over-denominator situation (i.e., *n/d*), *n*. the number of deaths, is relatively easy to record, but *d*. the number of vials sold or opened, is subject to inaccuracies and statistical question, and, of course, the morbidity associated with the use of contrast media is imponderable. Still, reports from Winthrop-Breon Laboratories on the intravascular use of iohexol (Omnipaque) worldwide indicate over 3 million doses (vials) sold with only nine fatalities (nine per 3 million or one death per 300,000). Four of these deaths were considered not to be drug related, four patients had severe cardiovascular disease, and one patient died from a technical error during cerebral angiography. Additionally, there have been reports of deaths in Great Britain from the intravenous use of iohexol (56). Schrott and colleagues from West Germany reported the largest series to date (50,660 patients) using a nonionic agent, iohexol, for intravenous urography (55). An overall reaction rate of 2.1% was achieved. Over hald of the patients (52%) had so-called risk factors; however, the precise nature of these risks was not well detailed. The rate of reactions was somewhat higher in this group — 2.7%. The types of reactions encountered in their experience were respiratory, .34% (n = 174); and cardiovascular, .22% (n = 110). The

severity of reactions was categorized as mild, 1.2%; moderate, .9%; severe, .01%; and fatal, 0% (55)! In the severe-reaction group, there were six patients. Epiglottic edema, shortness of breath, or decreased blood pressure and severe skin reactions occurred in these patients, but all were noted to have responded to treatment. Five of these 6 reactions occurred in patients *with* risk factors. For patients with *no* risk factors, these authors reported an incidence of only 1.3% for any and all side effects (55).

Reports on the use of iopamide (Isovue [Niopam, Bracco]) from Squibb Diagnostics show that with nearly 4 million doses there have been two reported fatalities associated with the intravascular use of iopamidol. There have been other reports of deaths related to iopamidol (25), Dawson, R. G. Grainger, personal communication, September 1986.

Mallinckrodt and Guerbet report close to 7 million doses of Hexabrix (ioxaglate) used worldwide since the late 1970s with only 28 deaths associated with its intravascular use (approximately 1/228.571). The major cause of deaths could not be directly linked to the contrast material itself and were in seriously ill or high-risk patients. Obviously, statistics based on any reporting system are subject to inaccuracy (e.g., under-reporting a limited data base (Mallinckrodt personal communication, October 1986). The newer agents are often used in patients thought to be at a higher risk, which must be carefully considered when the data on death rates with LOCM are assessed.

* * *

McClennan's Testimony, pgs. 102-103.

[102] Q. Left column. Would you explain the word osmolality?

A. The word osmolality appears in the sentence. Conray has an osmolality of such and such.

Q. Correct.

A. Osmolality is a physical measure of its lay terms. Osmolality is measured — it's the tenacity of — it's the tenacity of a compound. When a compound like Conray is put into a solution, the solution that is in, or put into water or the blood, it's a salt, like table salt.

Q. Umhum.

A. And it — remember in high school, chemistry with fun memories, I'm sure, it disassociates it, breaks it up into two particles, sodium methiodal and chlorates, same for Conray, goes into a solution and it breaks up as a salt into two molecules. By doing that, that increases the osmolarity of the solution, makes it in a physical sense, thicker, more — less physiologic, if I can, again, for purposes of explanation, put the measure of osmolality, that here says that a thousand in prospective blood or serum, that we have in — it measures three hundred; this measures a thousand, so it has a much higher osmolality than serum. So I don't know if I have explained that to you, the way you want it, but it's a physical measure or [103] physical property of a solution, measured against the standard, which we can all understand blood, much more irritative it's much more hypertonic than water or blood.

Q. Now, would you explain the term osmolality, which is used in the same paragraph.

A. What — it's considerable, osmolality, it's a measure of — it's how you measure osmolality, it's kilograms per water, per — kilograms slash H2 of water. Osmolality is a confusing measure that I'm, at the moment, I'm unable to more adequately explain what I just explained to you, that as you can

see, it's not as high as the osmolality. I don't know precisely the physical chemistry, the measurement of — of why the measurement is different, if that's what you're getting at, so I really can't — I can't give you a physical chemical explanation. But the same principal is true, the same effect when a contrast or a salt associates in the solution, it's still present. These salts, like Conray or any other, needlessly increase their osmolality, when they go into solution, and make them less physiologic, of course, than normal blood.

Q. Now, doctor, referring your attention to page six, left column —

A. Right.

Q. From the bottom up, the first line, can you explain what histamine sensitivity means?

McLennan's testimony in regards to package insert's doses approval by the F.D.A.

[42] United States, and specifically for contrast material, like the Conray-60 that we're talking about. Package insert is a description of the chemistry of the drug and designed to be a general guidelines for uses, precautions, indications; it's in many ways general, because the FDA and the legal system doesn't want to infringe on the art of medicine, of, for instance, you make a package insert, so restrictive, that nobody can use it, then you'll be denying perhaps the patient to benefit of the drug or medication. Package inserts, I can't tell you when they were — became law, but I mean, I have been dealing with package inserts since, again, back in — well, in mid '70's when I served on a committee, to examine a package insert; at the time we were trying to bring — make them more contemporary in turn of the doses, as contrast material used to develop the — continued to develop throughout the '70's, became apparent that we needed to give some patients more contrast, large doses. And some of the package inserts, strictly wouldn't let you do that, and every-

body was doing it. So in one way, it's better science to make the package insert reflect what was really the case, and second, it was tying the arms of some physicians, who were already giving more contrast, so —

Q. You personally, what was your involvement personally, in that study?

[43] A. On, in the study — the committee on contrast material safety for the ICR, International Congress of Radiology, excuse me, worked with the FDA, to examine the whole package insert for all of contrast material, and then specifically made recommendations which actually we published in Referee Journal, our recommendations, which were then subsequently adopted by the FDA.

Q. Excuse me, doctor, you said that this committee worked with the FDA. What is FDA?

A. I'm sorry, Food and Drug Administration. The committee met with their members and we discussed the issue because the FDA has the final say, of course. We made recommendations, published those recommendations and that was one of the main functions of the committee that I served on, was to prior change the package insert and make it more contemporary in terms of the dose.

Q. Let's interrupt here to change tapes.

(AT THIS TIME THE VIDEO TAPE WAS CHANGED.)

MR. LOPEZ:

Brother counsel, before the deposition continues, I would like to state for the record, to be able to preserve the issues so that the Honorable Judge Fuste may rule on this. We have had approximately twenty . . .

* * *

[52] be done. So it's a basic structure that is on purpose general, because if one gets terribly specific and restrict all the uses and indications, then you are not comtemporary, and

you're really now providing that benefit to the patient, that's the reason why that article that was just objected to was written, to make radiologists aware of what's going on.

MR. LOPEZ:

I object to the — going into the content of a document that has been objected.

BY MR. ESCALERA:

Q. Go ahead, doctor, the objection is noted. Go ahead.

A. I can answer?

Q. Sure.

A. I lost my train of thought, a bit, to get back —

Q. We were talking about what kind of —

A. The risk of repeating myself, remembering that repetition is the mother of learning. The essential guideline or basis for the package insert is to provide a structure, which is not too restrictive, so that the art of medicine can be practice, but that is contemporary and reflects what's current knowledge, reasonable and customary usage and reasonable risks and warning to the use of the material. What goes into making that document, it's the input that has been objected to, and the [53] general discussions and all of the signs, and the reams of papers that investigators like me collect on the drugs, so that the FDA can fulfill its duty, legal or not duty, it's duty to society, to forewarn for reasonable risks and also be contemporary in terms of what it reflects, so a doctor who isn't very used to it, or technologist or a nurse who might not have intensive medical training, could read the document, it's in, its written — in sort of more lay language than a scientific article, so that even a general practitioner could understand the interest of the use of the drug.

Q. Okay. Doctor, in terms of day to day practice, how effective or how valuable are the inserts? Is there a day to day practice for a radiologist; we are talking about inserts for radio contrast material in particular.

A. For — to be honest with you, for day to day value, they are probably not very valuable.

Q. Why?

A. By that I mean that every radiologist or even somebody that is supposed to not be the average, which is supposed to be in charge and know the field, like me. He doesn't read it every day. Most of them are read; most of the knowledge is almost common knowledge amongst people that are very familiar with contrast material, and the value is whenever there is a new indication [54] in change and use. You can increase the dose, or a new reason to issue a warning, manufacturer and FDA sends out new guidelines, updates the package insert, and that becomes the new package insert. That's brought to the attention of most radiologists, but in the day to day practice, it's not referred to, — largely because of what I said earlier, I think in this testimony, that is, these kind of compounds have been used for almost thirty-five years; the education system about their use, when I teach about this, all the things I teach to residents are in the package insert. So I don't know if that answers —

Q. Yes.

A. — your question, but that's —

Q. I would like to go now, doctor, into — a little bit into what is called risk condition for the application of contrast material, or for the injection of contrast materials. Can you tell us what conditions, if any, are known to present additional risks in the use of contrast material or Conray-60 in particular?

A. There is several conditions that are known to represent a risk. I'll be as general as I can, and answer the easy risks first. Almost all of the general well known risks are listed in the package insert, and they have to do specifically with people who have previous — have had previous contrast material, like Conray-60, and who have had some sort . . .

* * *

[357] DR. EDWARD M. ATEN having been duly sworn, testified as follows:

THE CLERK: Sir, will you please state your full name and spell it for the record.

THE WITNESS: Edward M. Aten.

DIRECT EXAMINATION

BY MR. ESCALERA:

Q. (By Mr. Escalera) Dr. Aten, where do you live?

A. I live in St. Louis, Missouri.

[358] Q. Where do you work?

A. I work for Mallinckrodt.

Q. Could you please state your academic and professional background, doctor.

MR. LOPEZ: Your Honor we would request the same ruling from the Court. He just said what is expert is, and that would be sufficient.

THE COURT: Tell us about your expertise, and there is a stipulation that you are qualified. What is your expertise?

THE WITNESS: I am a physician trained in internal medicine.

Q. (By Mr. Escalera) What is your position at Mallinckrodt?

A. Medical director.

Q. What are your duties at Mallinckrodt?

A. I have two departments that report to me. One is the medical department and the second is the regulatory affairs department.

In the medical department, we have two primary responsibilities.

THE COURT: Come closer to the microphone.

THE WITNESS: We have two primary responsibilities. One to do clinical research on new products and the second is to monitor adverse reactions with the products that are [359] already on the market.

The regulatory affairs department is responsible for dealing with FDA and to seeing that all of our products that we are selling conform to U.S. regulations.

Q. (By Mr. Escalera) What is FDA, doctor?

A. That is the Food and Drug Administration.

Q. And that is what?

A. That is a branch of the U.S. Federal Government that is responsible for governing and regulating pharmaceutical products that are on the market.

Q. How many persons do you have working for you in those departments, doctor?

A. We have 22 professionals in our department. Of those, we have two physicians. One is a nuclear medicine physician. The other is a surgeon.

Q. Can you tell us the names of those two physicians?

A. Yes, doctor Dibis Fowler is the surgeon, Mayo Clinic and doctor Miriam Denamore is the nuclear medicine radiologist.

Q. If I were to ask you, doctor, who, in Mallinckrodt, is responsible for working to assure that the package insert corresponds to accepted medical knowledge, who would you say is that person?

A. I have primary responsibility since I am over that department.

In addition to that, I have a fellow by the name of [360] Chris Piper, who is our director of regulatory affairs and is expert in regulations. And, also, the two physicians in my department also monitor the safety of the product.

Q. Could you please, doctor, explain, for the benefit of the members of the jury, the product history of Conray 60, in particular.

A. Okay. Conray 60, the new drug application for Conray 60 was submitted to the FDA in December of 1981.

That particular application included information with respect to the chemical structure of the product, the stability, animal testing, and those types of information.

Then, in addition to that, it included clinical studies which consisted of over a thousand patients at six major medical centers in the United States.

Q. What are the benefits of the product, doctor?

A. Well, Conray has been considered a, really, a premium product since its introduction in 1962. It has been the principal product for the last 25 years that is used by neuroradiologists.

The other primary agent that has been on the market is a diophrisowate. And they generally consider Conray to be a much safer product.

Q. Okay. Can you tell us, doctor, what is the role of the Food and Drug Administration and the approval of the product?

A. Okay. Well, we pretty much being in the pharmaceutical [361] industry, live and die with the Food and Drug Administration. Because, obviously, everything that we do is very closely regulated with the agency, the Food and Drug Administration. And because of that we maintain a relationship with them in the fact that we want to be credible and want them to trust us. So we have a fairly open relationship with them.

Now, in order to get a new product on the market — Can I go through that process?

Q. Yes.

A. To make you can understand a little bit more as to how we would do that.

Generally, a product is tested in animal studies for one to two years before it is introduced into any human clinical studies.

At the time that we are going to do a clinical study, we prepare all of the information that we have, both the chemistry data and the animal data. And along with that we submit to FDA our clinical plan as to how we are going to study the drug.

That consists of three phases of clinical research.

The first phase is a phase where you really only do one study and monitor very carefully at small dosages. Because it is the first time that a drug goes into a human being. And you monitor how the drug is absorbed and how it is distributed through the body, how it is metabolized and . . .

* * *

[373] Q. What would happen in terms of the patients that should undergo that treatment?
A. Well, that is, potentially, if you put a million adverse reactions in there you will simply scare a doctor from using a product, when the benefits might out weigh the risks. If they see a package insert that literally has thousands of things, they won't use the products.
Q. And what about the Food and Drug Administration, what would happen if you try to do that?
A. Well, as I said before, Food and Drug Administration has to approve those changes and you simply wouldn't permit it to start listing things that were totally theoretically unfounded.
Q. Doctor, I want to show you a book, and ask you to tell us if this —

THE COURT: Have it identified.

MR. ESCALERA: The book is Contrast Media Biological Effects and Clinical Application.

MR. LOPEZ: May I talk to counsel?

THE COURT: Of course.

MR. ESCALERA: Sure.

THE COURT: Identification?

THE CLERK: C, your Honor.

THE COURT: C?

THE CLERK: C. Defendants.

* * *

[387] A. Yes.
Q. Now, did, does hexibrix have, is it ionic or nonionic?
A. Ionic.
Q. Ionic?
A. It is ionic.
Q. Yes. And does it have a lower osmolality than Conray?
A. Yes.
Q. Also is lesser hypertonic than Conray is, right?
A. That is true.
Q. And isn't it true, sir, that it is less dangerous than Conray?
A. No, sir, that is not true.
Q. Do you have the literature of the product, the advertisement literature? Your company published it.
A. I have the literature for all of them.
Q. Can I have it made available, please?
A. Certainly. Which one do you want?
A. The advertisement that is placed on hexibrix.
THE COURT: Advertisement or package.
MR. LOPEZ: No, in the advertisement, your Honor. This is Omnipaque.
THE WITNESS: Which do you want?
MR. LOPEZ: Hexibrix, the one that is manufactured by Mallinckrodt.
THE WITNESS: I don't think if I have that. Wait, [388] yes, I do.
MR. ESCALERA: Your Honor, excuse me. Are we talking about insert or advertisement.
MR. LOPEZ: Advertisement.
Q. (By Mr. Lopez) Isn't it true, doctor, that products that reduce osmolality may be associated with better patient tolerance and a reduced incidence of adverse reactions?
A. The agents are approved — the only advantage that —
Q. May I interrupt, doctor?
A. Yes.
Q. I would request a yes or no answer.

THE COURT: Impossible to have a yes or no answer to that.

MR. LOPEZ: Very well.

Q. (By Mr. Lopez) Go ahead.

A. I explained earlier that FDA approved comparative statements. The only advantage that is approved for hexibrix is less heat and pain.

Q. What?

A. Less heat and pain on injection.

Q. So you don't agree with the statement that it may be associated with better patient tolerance and a reduced incidence of such adverse reaction when you have a product with reduced osmolality.

A. There are a number of people that feel that that is [389] true. But it hasn't been established. All of the manufacturers would like to establish that because it would be a very important claim if we could do that.

Q. Now, doctor, as to histamine and complement, allergic like reactions may also be the result of chemical toxicity. These reactions range from mild hives to life threatening anaphylactoid shock.

A. Yes.

Q. Do you disagree with that statement?

A. Yes.

Q. Yes?

A. Yes.

Q. Those and others have shown that ionic statements stimulate histonic release and complement activation.

A. May I see the book I read. No the other book the one that —

THE COURT: Identified as the gray book.

MR. ESCALERA: Yes, it is C.

MR. ESCALERA: Your Honor, for clarity for the record, can we know from where is Brother Counsel reading?

MR. LOPEZ: Nonionic Omnipaque. This is the one I just read to him.

THE WITNESS: This is from the book I introduced to you earlier. The answer is yes, to be provided, but some conclusions can be drawn. Basophil degranulation with [390] resultant histamine release occurs in the presence of iodinated contrast material. There is both in vitro and in vivo evidence to substantiate this claim. Nonionic agents appear to have the same histamine releasing capability as ionics in vitro.

In vivo work has not yet been done for nonionics. So that is not an established fact.

I will admit that Sterling Winthrop is trying to convince physicians of that, and there are a couple of studies that suggest that it is true. But the general experts in this area do not agree with that position.

Q. (By Mr. Lopez) Doctor, do you agree with this statement: "The solution to this problem would be to directly warn the patient of the drug effects and dangers so that the patient could be observed for the early signs of a reaction and withdraw from the drug or take the precautions to prevent the injury. The manufacturers have concertedly resisted this approach of warning consumers about drug dangers because of fear of the effect upon drug use. The FDA has recently started serious investigation of the possibility of a package" —

THE COURT: Is this a question — What is this?

MR. LOPEZ: Whether he agrees with the statement.

THE COURT: You are reading from where?

MR. LOPEZ: May I show it to your Honor?

[391] THE COURT: Where did you get this from? What is this?

MR. LOPEZ: From one of the books, your Honor.

THE COURT: Well, which book?

MR. LOPEZ: I don't know —

THE COURT: This is a Lawyer's book or doctor's book or what?

MR. LOPEZ: Products liability book, your Honor.

THE COURT: For lawyers.

MR. LOPEZ: Yes, your Honor.

THE COURT: How dare you read from this as if it was —

MR. LOPEZ: I am asking the question —

THE COURT: This is not proper.

MR. LOPEZ: Very well, we withdraw the question. Let me ask you now.

THE COURT: You are testifying that is what you are doing.

MR. LOPEZ: May I —

THE COURT: Don't do it again.

MR. LOPEZ: Your Honor, I am reading from —

THE COURT: No, no, you ask questions the proper way, not that way.

Q. (By Mr. Lopez) Doctor, Do you agree with the statement: "Ionic agents, due to their chemical structure and [392] hyperosmolalities, may disrupt an intact blood-brain barrier, essentially negating its protective function and enter the central nervous system?"

A. That is ridiculous. We have got the package insert here and have reviewed it. I think we can establish that.

MR. LOPEZ: Can I show it to the witness, your Honor?

THE COURT: Mark it as identification.

Q. (By Mr. Lopez) Did you read it?

A. Yes, sir.

Q. So your statement to the Ladies and Gentlemen of the Jury is that that statement made by Omnipaque is ridiculous.

A. This issue is before FDA right now. This is an advertisement for a product that is about a $100 million a year to this company. And they are making comparative claims that are not approved by FDA.

And, in fact, we have the Omnipaque package insert here and I would challenge you to define anything in the package insert that would suggest that this is true. It is totally unsubstantiated.

Q. Doctor, for Mallinckrodt, how many millions of dollars does Conray make?

A. Boy, I would guess it is a $10 million product.

Q. Now, doctor, addressing — with ten million — No, I withdraw the question.

APPENDIX E

JOINT REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS AND THE COUNCIL ON MEDICAL SERVICE

(I-90)

Subject: Radiographic Contrast Media

Presented by: William C. Scott, MD, Chairman
Council on Scientific Affairs and
Grant V. Rodkey, MD, Chairman
Council on Medical Service

Referred to: Reference Committee E
(Hugh E. Stephenson, Jr., MD,
Chairman)

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all of the factors and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and patterns of practice evolve. This report reflects the views of scientific literature as of June 1990.

Introduction

The following joint report of the Council on Scientific Affairs and the Council on Medical Service is written in response to Substitute Resolution 25, which was adopted at the 1989 Interim Meeting. It asked the AMA to study the pricing policies of manufacturers and distributors of the new nonionic contrast media. Substitute Resolution 25 was based on a concern that use of low osmolar contrast media (LOCM) placed a heavy financial burden on payors, providers, and patients. The price differential between LOCM sold in the

U.S. and abroad and the reluctance of manufacturers and distributers to provide information justifying the high cost of LOCM in the U.S. were additional concerns expressed in Substitute Resolution 25.

Diagnostic imaging procedures, such as intravenous urography, computed tomography (CT) and angiography, are performed using intravascularly administered contrast agents whose iodine content imparts radiopacity. The media currently in widest use in the United States, the so called high osmolar contrast media (HOCM), have been available for nearly 40 years. High osmolar contrast agents such as iothalamate meglumine (Conray-Mallinckrodt) and diatrizoate meglumine (Hypaque-Winthrop and Renografin-Squibb) are characterized by osmolarities of up to seven times that of plasma. Although HOCMs are considered one of the safest of drugs, the high osmolarity of these agents is associated with undesirable physiologic effects in some patients.[1]

Concern over the toxicity of HOCMs led to efforts to develop contrast media with lower osmolarity. In 1978, the first commercially available LOCM (metrizamide) went on the market. Today the four low osmolar contrast media in routine use in the United States are: iohexol (Omnipaque, Winthrop Pharmaceuticals), iopamidol (Isovue, E.R. Squibb and Sons, Inc.), ioversol (Optiray, Mallinckrodt, Inc.), and ioxaglate meglumine sodium (Hexabrix, Mallinckrodt, Inc.). These agents are also referred to as nonionic contrast media. However, it should be noted that ioxaglate is really an ionic dimer. (The literature alternates between the use of the terms LOCM and HOCM and nonionic and ionic when referring to the two classes of contrast media. In this report the terms LOCM and HOCM will be used unless a study referred to in the report specifically uses the terms ionic and nonionic). All of the LOCM agents average twice the osmolarity of plasma.[2]

The quality of the image produced using contrast media is dependent on the quantity of iodine administered rather than on the chemical composition of the medium itself. LOCM

and HOCM produce diagnostic images of similar quality. The media differ however in price and in the rate of adverse reactions associated with their use. In comparison to HOCM, LOCM are characterized by lower rates of mild, moderate, and severe reactions in patients. LOCM also are significantly more expensive than HOCM, with prices that are approximately 10 times higher.

TABLE 1: PRICING OF SELECTED CONTRAST MEDIA

DRUG		PRICE*
Low Osmolality		
Iohexol (Omnipaque-Winthrop)	non-ionic	$105.81
Iopamidol (Isovue-Squibb)	non-ionic	$ 89.88
Ioxaglate (Hexabrix-Mallinckrodt)	ionic	$101.20
Ioversol (Optiray-Mallinckrodt)	non-ionic	$ 87.00
High Osmolality		
Iothalamate Meglumine (Conray-Mallinckrodt)	ionic	$ 13.63
Diatrizoate Meglumine		
(Hypaque-Winthrop)	ionic	$ 10.81
(Renografin-Squibb	ionic	$ 12.07

*Price is to pharmacist for 100 ml, a typical dosage for computer enhanced tomography, based on listings in *Drug Topics Red Book, 1989* for direct purchase from manufacturer.

Although on a per procedure basis, the difference in cost between HOCM and LOCM may not be viewed by the patient or the physician as that substantial, universal conversion to LOCM for all procedures has significant economic consequences for patients, hospitals, radiology practices, and for the nation's health care system. Because the additional cost of LOCM is often not covered by insurance at this time,

hospitals and radiology departments face significant added expenses in converting to LOCM.

The following report discusses the morbidity and mortality of low and high osmolar imaging agents, the risks associated with the use of each agent in specific classes of patients, and the financial implications of converting to universal use of LOCM. The report concludes with policy recommendations concerning the use, reimbursement, and pricing of LOCM.

Chemistry of Contrast Media

Contrast media are often described by the ratio of radio-opaque iodine atoms to osmotically active particles in each molecule of the medium. All contrast media typically disassociate in solution into the iodine containing component and various osmotically active components. For example, the conventional HOCM are often referred to as "ratio 1.5 media" because there are three iodine atoms for every two osmotically active particles. The iodine to osmotic ratio of LOCM is 3.0 and thus the osmolarity is reduced by 50 percent for equivalent iodine concentrations. The ionic dimer, ioxaglate, accomplishes this by increasing the number of iodine atoms, whereas the nonionic agents iohexol, iopamidol and ioversal reduce the number of osmotically active particles.[2]

Adverse Reactions

Contrast media induce a wide variety of physical responses. Hemodynamic alterations resulting in changes in cardiac performance, alterations in renal function, depression of the central nervous system, and pain at the injection site have been described.[3] Frequently reported systemic reactions include pain at the injection site, a metallic taste, flushing, and nausea and vomiting. Overall, the reported frequency of adverse reactions to HOCM varies widely in the published literature. This variation reflects differences in the types of radiologic

procedures performed, the definition of an adverse reaction, and the number of risk factors identified in the studied patients. Shehadi has reported the overall incidence of adverse reactions to be slightly less than 5%, whereas Moore, et. al., in a prospective study of 795 patients, reported that mild, moderate and severe reactions occurred in 45%, 5.5% and .4% of patients respectively.[4 5] The inclusion of heat and pain as adverse reactions and the inclusion of patients' subjective experience may be responsible for the high reported incidence of adverse reaction in Moore's study.[5]

In 1982, Shehadi and Hartman in separate studies reported that fatal adverse reactions are extremely infrequent, occurring in only 1 in 5,000 to 70,000 procedures using HOCM.[4 6] However, more recently, the final results of a large scale Japanese Study have been reported in the June 1990 issue of Radiology.[7] The 337,647 cases were divided into two groups, one receiving low ionic and the other receiving high ionic media. There was only one death reported in each group. Neither death could be attributed to the contrast agent. These results differ from the previously mentioned rates of fatal reactions and attest to the safety, in terms of fatal reactions, of both classes of contrast media.[7]

Mild systemic effects are well tolerated or respond quickly to treatment. Specific organ effects are transitory and usually not clinically significant unless a patient is already compromised. For example, injection of contrast medium can precipitate an acute decline in cardiac function in patients whose cardiac function is already compromised.[1] Acute renal failure associated with injection of contrast medium is a frequently cited concern, but this occurs rarely and only when there is preexisting renal disease coupled with poor hydration.[3]

Numerous studies have demonstrated that the mild to moderate adverse reactions to contrast media can be reduced when using LOCM.[8 9 10] In a review of 100 randomized controlled trials which studies relative safety of the two agents,

Kinnison reported that heat sensation occurred less frequently with LOCM and pain occurred less frequently only when the LOCM was injected intravenously. HOCM was associated with greater cardiac abnormalities including increased or decreased heart rate, increased left ventricular end-diastolic pressure, decreased systolic pressure, and QT prolongation, depending on route of administration. No differences between the two classes of media were seen in the incidence of nausea, vomiting, urticaria, bronchospasm or neurologic events.[10]

Risk stratification schemes attempt to identify those patients at highest risk of an adverse reaction, both to take special precautions and, more recently, to identify those patients who would benefit most from using LOCM. Identified risk factors include a previous adverse reaction to contrast media, a food and/or drug allergy, asthma, renal or cardiac impairment, poor hydration, diabetes mellitus, multiple myeloma, and sickle cell anemia. Infants and small children are also considered a high risk population.[11 12 13] The risk of reaction is twice as great in those who have a history of allergy and three to four times as great in those who had a previous adverse reaction to contrast media.[1] On the other hand, only 15 to 16% of patients with an initial adverse reaction to contrast media experience a repeat reaction upon reexposure.[4]

Of greatest concern to radiologists is the comparable incidence of severe life-threatening reactions in LOCM and HOCM. However, this type of comparison requires large numbers of patients in order to demonstrate a significant difference in such an uncommon event. Recently, three large-scale studies addressing this issue have been completed. Those studies are referred to the literature as the Palmer, the Katayama, and the Wolf studies.[11 14 15]

F. J. Palmer Study

Palmer studied the adverse reactions reported in 109,456 examinations performed in Australia and New Zealand which

used either ionic or nonionic contrast media. Patients were assigned to either a low or high risk group based on a variety of clinical conditions. High risk patients were defined using the 1986 RACR suggested guidelines. These patients included those who had a previous reaction to contrast media, patients who had asthma, a significant allergic history (not to drugs), renal or cardiac impairment, poor hydration, diabetes mellitus, myelomatosis, sickle cell anaemia, and infants and small children. Severe reactions in the Palmer study were defined as "urgent therapy required and considered at risk; hospital admission required." Moderate reactions were defined as "require therapy but not considered at risk; outpatients do not require hospital admission" and mild reactions included "all skin reactions, no therapy required, does not include sensations of heat."[11]

Patients in the high risk group received nonionic contrast media, and those in the low risk group received ionic contrast media. The incidence of severe reactions was .09% in the low risk group and .03% in the high risk group.[11]

H. Katayama Study

Katayama reported on a large scale prospective study in Japan which compared the rates of adverse reactions in a sequential fashion as participating hospitals converted from using the ionic agents to nonionic agents. A total of 337,647 cases were studied; half received ionic media and half received nonionic media. The overall incidence of adverse drug reactions was much lower for nonionic media group (3.13%) than for the ionic media group (12.66%). In the Katayama study, severe and very severe drug reactions were defined as dyspnea, sudden drop in blood pressure, loss of consciousness, dyspnea and cardiac arrest, various combinations of these reactions, and death. Less severe and mild drug reactions were defined as nausea, urticaria, itching, heat sensation, vomiting, flushing, sneezing, and hoarseness.[7]

In contrast to Kinnison's review, Katayama reported that the incidence of each specific type of adverse drug reaction, including nausea, vomiting and urticaria was lower with nonionic media. The overall incidence of severe and very severe drug reactions was .22% with ionic contrast media and .04% with nonionic contrast media. Those patients with a history of allergy (i.e., at high risk) had a .10% incidence of severe reactions with nonionic agents while those patients with no allergy history had an .18% incidence of severe reactions when exposed to ionic agents.[7]

G. Wolf Study

Wolf and colleagues also reported on a prospective trial conducted in the United States. This trial involved 6,006 consecutive patients who received ionic agents and 7,170 consecutive patients who received nonionic agents. The patients were not stratified into high and low risk groups. Patient reactions to contrast media were classified as either minor, moderate, severe, or death. Severe reactions included loss of consciousness, cardiac arrest, shock, or symptomatic cardiac arrhythmia; moderate reactions included faintness, severe vomiting, extensive urticaria, facial or glottic edema, dyspnea or bronchospasm, chest or abdominal pain, and severe headache; minor reactions were nausea, itching, mild vomiting, and limited urticaria. Wolf reported that there was a 1.3% incidence of severe reactions requiring treatment in the ionic group versus .2% in the nonionic group.[13 15]

These three studies currently form the clinical basis of discussions supporting the universal use of LOCM.[16 17] In particular, the Katayama and Palmer studies indicate that there is a greater risk of severe reactions if the patient has no risk factors and receives a HOCM versus a high risk patient who receives a LOCM. However, many third party payors have resisted universal use of LOCM due to their high price and the very low incidence of severe, life threatening adverse

reactions with either class of contrast media. The result is an ethical dilemma for radiologists, who now must choose between two classes of contrast media with similar effectiveness but with differing safety and cost profiles.

Pretreatment with Corticosteroids

Whether pretreating patients with oral corticosteroids can reduce the incidence of reactions to ionic media to the level of reaction to nonionics has been evaluated in two studies with somewhat different results. Lasser, et. al., found that pretreating patients with two doses of oral corticosteroids significantly reduced the incidence of most reactions to the ionic media. This frequency of reaction approximated the frequency of reactions to nonionics published in other studies.[18] However, Wolf et. al. reported that with ionic media plus steroid pretreatment (2 doses), reactions occurred 3.90% of the time compared to 0.67% reactions with nonionic media alone, allowing them to conclude that use of the nonionic agents was significantly safer than ionic agent alone or the ionic agents with corticosteroid pretreatment.[15]

Cost Per Procedure and Economic Impact of LOCM

LOCM cost about 10 to 20 times per procedure more than HOCM depending upon the drug used and the procedure performed. The per procedure cost of conventional HOCM varies from around $4.95 (for intravenous urography) to $23.40 (for coronary angiography). LOCM costs per procedure range from around $45.50 (for intravenous urography) to around $178.20 (for body CT) (see Table 2).[19]

TABLE 2: COST OF HOCM AND LOCM FOR COMMON DIAGNOSTIC PROCEDURES, 1986

Procedure	Cost of Contrast Material/Procedure		
	HOCM	LOCM	Increase in Cost
Head Computed Tomography (CT)	$ 8.30	$134.55	16X
Body CT	13.25	178.50	13X
Coronary Angiography and left ventriculography	23.40	149.74	6X
Intravenous urography	4.95	45.50	9X
Carotid arteriography	8.30	134.55	16X
Digital study (intravenous injection)	9.80	178.20	18X
Peripheral arteriography	9.80	178.20	18X

Source: Ronald G. Evans, M.D., "Economic Impact of Low-Osmolality Contrast Agents on Radiology Procedures and Departments," *Radiology*, January, 1987; 162:268. Cost and charge information is from the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.

Although LOCM account for a relatively small proportion of the contrast media market in the United States, its use is growing. In 1986, about 9% of those radiological exams requiring contrast media were done with LOCM. The following year, this percentage climbed to 15% and currently an estimated 25% of the 10 million vascular, computed tomography, and intravenous urography exams annually performed in the United States involved LOCM. Estimates of the current market for HOCM and LOCM agents in the United States range from $300 million to $550 million.[20 21] If the

United States switched to universal use of LOCM, this figure is expected to increase to $1 billion.[22]

Cost Containment and Risk Management Strategies

To better manage both the cost and the risks associated with the use of contrast media, physicians have actively sought more efficacious ways of using LOCM agents and safer ways of using HOCM agents. Based on the Katayama and Palmer data, more and more physicians have become unwilling to use risk stratification schemes to manage the use of HOCM and LOCM agents. Instead they have attempted to control contrast media costs by avoiding unnecessary waste when performing procedures and by substituting, when possible, alternative diagnostic tests for those requiring contrast media.

A 1983 Canadian study of intravascular contrast media use at three southwestern Ontario hospitals found that although some wastage of contrast media may be inevitable, a portion of wastage could be avoided if multi-dose dispensing systems and a variety of bottle sizes are used.[23] Contrast media products are available in the United States in a variety of concentrations and vial and bottle sizes. Optiray (ioversol), for example, is marketed in concentrations of 320, 240 and 160 (mg Iodine/ml), in vial sizes of 25 ml, 30 ml and 50 ml., and in bottle sizes of 100 ml, 150 ml, and 200 ml.

Hospital costs associated with the use of LOCM may also be decreased by using less of the media to perform certain tests. After converting to universal use of LOCM agents, Hamilton General Hospital, Hamilton, Ontario, Canada, initiated a program aimed at saving contrast agents by substituting noncontrast procedures for contrast procedures and by reducing the amount of contrast agents used per procedure. As a result of this program, the hospital reportedly saved 23% of the volume of contrast agent it expected to use over a one-year period.[24] According to Dr. James Zelch, director of radiology at the Cleveland Clinic-Florida in Fort Lauderdale,

Fla., the usual 60 to 100 cc dose of conventional or HOCM contrast solution per procedure used in urography exams can be decreased when nonionic agents are used. This reduction may be done without compromising image quality regardless of the patient's weight or creatinine levels.[25]

These clinical stretegies are some of the ways that physicians can promote patient safety and the efficient use of contrast agents. The financing of LOCM, however, is a health system payment issue that lies largely beyond the control of the individual practitioner.

Reimbursement for LOCM

Third-party payment policies for LOCM are changing. In August 1987, and again in January 1989, Winthrop Pharmaceuticals, a manufacturer of both LOCM and HOCM agents, surveyed third-party payors concerning their reimbursement policies for radiographic contrast agents. The Winthrop survey found that over the two-year period, insurance coverage for LOCM had improved somewhat. Commercial insurers offered the most favorable LOCM reimbursement policies. According to the 1989 survey, 21 of the 23 commercial insurers participating in the survey stated that they made additional payments for some, if not all, procedures where LOCM agents were administered. Blue Cross and Blue Shield plans registered the greatest change in reimbursement policies over the period. In 1987, only 13 Blue Cross/Blue Shield plans stated they made additional payments for LOCM; by 1989, 42 plans stated that they recognized the additional costs associated with LOCM in their insurance payments.[26]

Governmental health care coverage for LOCM lags behind private coverage. Medicare is the principal health insurance program for the nation's elderly, the age cohort with the highest incidence of severe adverse reactions to HOCM. Most LOCM usage in the United States is for patients 40 to 70 years of age.[25] Medicare Part A covers hospital inpatient procedures

for persons age 65 and over and reimburses providers according to a prospective pricing system which is based on diagnostically related groupings or DRGs. The cost of imaging agents is included in the DRG payment for the diagnostic procedure performed. Although every year the Health Care Financing Administration (HCFA) makes adjustments to DRG weights to reflect changes in treatment patterns and new technologies, to date no DRG makes an allowance for the cost of LOCM. Medicare Part B covers procedures performed in outpatient and freestanding facilities. Only 17 of the 42 Medicare Part B carriers make some additional payments for LOCM. States in which Medicare B carriers provide payment policies for the additional cost of LOCM for radiologist's claims are:

Arizona (Aetna)
California (Transamerica Occidental Life Insurance Company and Blue Shield of California)
Colorado (Blue Cross/Blue Shield of Colorado)
Connecticut (The Travelers Insurance Company)
Georgia (Aetna)
Hawaii (Aetna)
Iowa (Blue Cross/Blue Shield of Iowa)
Kansas (Blue Cross/Blue Shield of Kansas)
Kentucky (Blue Cross/Blue Shield of Kentucky)
Minnesota (The Travelers Insurance Company and Blue Cross/Blue Shield of Minnesota)
Nebraska (Blue Cross/Blue Shield of Nebraska)
Nevada (Aetna)
North Carolina (Equicor)
North Dakota (Blue Cross/Blue Shield of North Dakota)
Ohio (Nationwide Mutual Insurance Company)
South Carolina (Blue Cross/Blue Shield of South Carolina)

South Dakota (Blue Cross/Blue Shield of South Dakota)
West Virginia (Nationwide Mutual Insurance Company)
Wisconsin (Wisconsin Physicians' Service Insurance)[26]

The cost of LOCM remains the chief barrier to their broader use.[27-30] Some hospitals and radiology services have instituted policies which limit the use of LOCM to high risk patients.[31 32] Even where there are no official policies on the use of LOCM, radiologists often consider the price of these drugs, as well as the patient's risk status, in deciding which contrast media to use. This is borne out by surveys of radiologists. In 1988, the *Administrative Radiology Journal (AR)* sponsored a national survey of hospital imaging departments and radiology facility directors. Ninety-two percent of the respondents to the AR survey agreed with the statement, "If low-osmolar media were not so expensive, they would completely replace the use of conventional media in most if not all procedures requiring intravascular contrast media"; 75% agreed "that low-osmolar contrast agents are diagnostically equivalent or superior to conventional media; and 68% of the respondents agreed that low-osmolar media offer significantly less risk of serious reaction.[33]

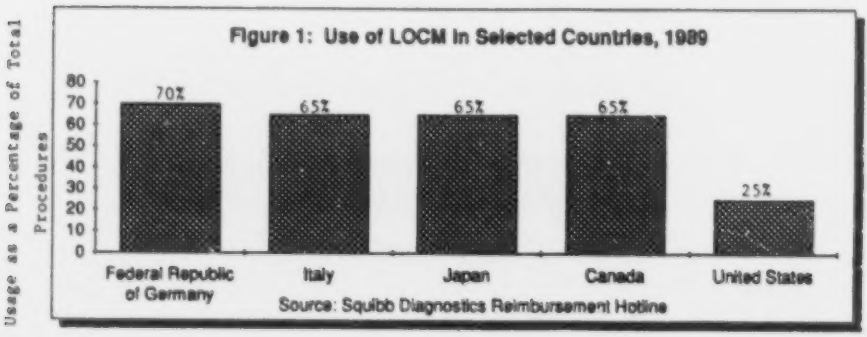
The AR survey was conducted prior to the release of the results of the Katayama, Palmer and Wolf studies. Since the results of these major clinical trials have been published, support for LOCM as a safer contrast agent has grown. Nevertheless, the use of low osmolar media is still restricted largely due to their price.[29]

Financial Impact of LOCM on Radiology Practice

In the absence of expanded health insurance reimbursement, increased use of LOCM is expected to have a signifi-

cant financial impact on hospitals and radiology departments. For the individual hospital or radiology department, increased use of LOCM represents a significant added expense that cannot necessarily be passed on to patients. Contrast media cost at one major regional facility increased more than 20 fold between fiscal years 1987 and 1989, rising from $23,500 to $595,000, while over the same period the number of radiology procedures performed using contrast media increased 20%.[21]

Other countries have adopted policies which permit more expanded use of LOCM than currently exists in the United States (see Figure 1). The price of LOCM is also reported to be somewhat lower overseas and in Canada than it is in the United States.[22]



The Health Council of the Province of Alberta, Canada, for example, declared that effective November 1, 1986, only nonionic or low osmolar contrast agents should be used for diagnostic purposes and the violation of this "by law" would be regarded as unethical conduct.[33] In September 1989, the Drug Committee of the German Medical Society made a simlar announcement endorsing the use of nonionic contrast media for all x-ray examinations and examinations of blood vessels in which a contrast media is used.[34]

Ioxaglate, an ionic LOCM medium, costs around $80 per 100 ml., in Canada and a little over $100 per 100 ml. in the United States. In Britain, the cost of LOCM is reportedly half that of Canada. Differences in pricing between countries may relate to differences in import duties, licensing fees, and other manufacturing costs.[33] In all countries, however, there is a substantial price differential between HOCM and LOCM and the impact of the high cost of LOCM on the health care system both in the United States and elsewhere has led many to question whether this price differential is justified. To date, there has been little detailed information from drug companies on the cost of developing, manufacturing, and distributing LOCM. Factors which have been cited by drug companies as contributing to the cost of LOCM include the relatively high cost of manufacturing these drugs and the necessity of recouping high research and development costs before the patents on these drugs expire.[21 35]

According to Marc Mayer, marketing director for Squibb Diagnostics, the molecular synthesis of LOCM is more complicated for LOCM than for HOCM: "It takes six times as much raw material to yield a comparable amount of finished product ... [and] instead of half a dozen synthesis steps, which are very basic for the ionics, there are more than 20 steps for a nonionic like Iopamidol".[35] LOCM agents require six or eight washes for purification instead of the one or two required for HOCM and the manufacturing process for LOCM lasts for three or four weeks instead of the two or three days required by HOCM.[35]

For companies that license contrast agents from European developers and import the basic chemical ingredients of these agents from overseas, there are additional costs of royalties, duties and finishing costs. United States companies also seek to recoup high research and development costs in the pricing of these drugs. According to William Mercer, vice president of marketing for Mallinckrodt, the capital investment cost for Optiray (ioversol), was more than $21 million. Gaining fed-

eral Food and Drug Administration approval is also cited as contributing to the cost of these agents.[35]

Most of the older HOCMs went off patent in the 1970s and once off patent, real prices for these drugs declined to as much as 60% of list price. The market for contrast medium was fiarly stable and drug companies sought market share largely by competing on price.[21] The large scale commercial introduction of the low osmolar contrast agents in 1986 changed the market for contrast media. Nonionics had already been marketed in Europe for several years prior to their introduction to the United States and there was mounting clinical evidence that these agents reduced the side effects that sometimes accompanied the ionic agents. Manufacturers priced the new contrast agent products for value. Even though the new agents were only used in about 5% of contrast media procedures in the United States in the first year, their introduction at a significantly higher price than the HOCM caused the combined market for both classes of media to jump from $139 million to $220 million.[21]

Expanded or even universal usage of LOCM is not expected to affect their price in the short term. Although increased competition among drug companies and the manufacture of larger quantities of the media in response to growing demand, may bring about some reduction in price, the real break in price is expected to occur only when newer, less costly agents come to market. Second and third generation contrast agents are under development and some of these drugs (e.g. ioxilon developed by Milos Sovak, MD, a University of California, San Diego radiologist) are reportedly less expensive to manufacture than the LOCM already on the market.[21]

The current generation of LOCM agents will be going off patent in the next several years. The patents for Hexabrix (ioxaglate-Mallinckrodt) and Isovue (iopamidol-Squibb) expire in 1996. The Omnipaque (iohexol-Winthrop) patent expires in 1999. The patent on Optiray (ioversol-Mallinckrodt) was issued in 1983 and should expire in the year 2000.

Although the price for HOCm dropped when these agents went off patent, it is unclear whether the same will be the case for LOCM. Other brand name drugs which have recently gone off patent have experienced a rise in price as drug companies seek to maintain revenues in the face of competition from generic substitutes.

Manufacturers of LOCM argue that it is "unfair" to compare the pricing of nonionics with the pricing for ionics because the latter are "priced artificially low." According to Squibb Diagnostics, while the price of other medical products and drugs increased some 425% between 1974 and 1984, the price of ionic contrast media dropped 14% before inflation.[21] Efficiencies in manufacturing and market competition contributed to the initial drop and subsequent leveling off in price for most HOCM products over the past 15 years. In an effort to gain brand loyalty, some manufacturers discounted their HOCM in hopes that when physicians begin to convert to the use of LOCM agents they will purchase the new agents from the same supplier.[21]

Today, the market for ionic and nonionic media is about $550 million. To date, the manufacturers of the LOCM have not been willing to offer the drugs for anything less than list price. Although Optiray is priced slightly below already established low osmolar contrast media to gain some market share, manufacturers in general, seem unwilling to enter into a competitive price war. The marketing approach is rather to stress the safety of LOCM over HOCM and to gain market through the conversion of HOCM users to LOCM use.[21]

Although some radiologists remain optimistic that as the use of LOCM expands and the drugs go off patent, the price of these agents will fall, it is unlikely that LOCM will ever be available at the prices currently paid for HOCM. Some proponents of broader or even universal use of LOCM maintain that the true cost differential between HOCM and LOCM is not as great as it appears. The use of LOCM, it is claimed, can lead to cost savings by reducing incidences of mild, moderate, and severe reactions and in reduced liability risk.[17]

According to John Palmer, MD, "The use of nonionic media can reduce minor and moderate reactions, increase efficacy and allow an increase in patient throughput. The cost to treat a severe reaction is estimated to exceed $6,000. This cost will be reduced six-fold with nonionic media and the potential cost of litigation may be substantial when death occurs with an ionic medium".[17]

The question of how much cost savings is realized as a result of the reduction in adverse patient reactions when LOCM is used in place of HOCM was addressed by Powe, et. al., in a prospective study of 795 inpatients undergoing procedures in which they received intravascular injections of HOCM.[36] Four procedures were involved: cardiac catherization, peripheral angiography, head computed tomography (CT), and body CT. The resources used in managing HOCM induced adverse reactions were measured and the cost of these resources was estimated. Four hundred and five patients (51%) experienced adverse reactions to the HOCM: of these, 358 patients (45%) experiences mild reactions (e.g., flushing or nausea); 44 patients (6%) experienced moderate reactions (e.g., vomiting requiring at least two doses of an antiemetic or intravenous fluid); and three patients (0.4%) experienced severe reactions (e.g., anaphylactoid reaction, myocardial infarction, cardiopulmonary arrest, seizure, and death). One patient in the Powe study experienced respiratory arrest and died after receiving HOCM.[36]

Ninety patients needed treatment as a result of their reaction to the HOCM. The estimated cost of treating these patients was calculated as the sum of the cost of drugs, supplies, labor, and other ancillary services used to manage adverse reactions in the radiology suite, radiology department space costs to the hospital, the cost of hospital inpatient resources used to treat these patients, and professional fees (e.g., nephrologist consultant) associated with the management of adverse reactions.[36]

The average cost per patient for the treatment of adverse reactions to HOCM in the Powe Study was $1.07 to the radiology department and $5.83 to the hospital. An additional $12.93 per patient was billed to third party insurers as a result of HOCM induced reactions. Although the Powe study estimated a lower cost of treating adverse HOCM reactions than the Palmer study, the Powe Study also found that much higher costs were associated with the treatment of severe reactions (approximately $4,000) than with the treatment of moderate (approximately $116) or mild (approximately $6.50) reactions. The average additional time spent by a physician dealing with an adverse reaction in the radiology suite was less than two minutes. The difference in material cost of HOCM versus LOCM ranged from $93 for body CT to $179 for cardiac catheterization. The study concluded that the cost of treating adverse reactions associated with the use of HOCM did not offset the higher cost of LOCM. The issue of liability costs that could arise if a patient experiencing a HOCM induced reaction brought suit against the health care provider was not addressed in the Powe study. With the availability of both LOCM and HOCM, it appears that radiologists are being driven to use LOCM for medical/legal reasons.[37—40]

Policy Considerations

The difficulties faced by physicians in selecting which types of contrast agent to use led the American College of Radiology (ACR) to issue a set of guidelines for the use of high and low osmolar contrast media based on the assumed risk different patient groups faced with each media type. Issued in 1988, prior to the November 1988 release of the Katayama study results, the ACR guidelines advocated the use of LOCM contrast agents in patients designated as high risk because they:

- had a previous, significant adverse reaction to contrast media, or had a history of allergies or asthma;

- had cardiac dysfunction;
- were severely debilitated;
- were undergoing potentially painful exams, such as peripheral arteriography, external carotid arteriography and lower limb phlebography; or
- were undergoing exams such as digital angiography where inadvertent motion must be minimized to optimize image quality.

The ACR also approved sponsorship of a $2.3 million study of x-ray contrast in the United States. When the preliminary results of the Katayama contrast agent research were released in November 1988, (Katayama, 1988) representatives of the ACR reviewed the study and determined that the scientific design and statistics were valid. Based upon these conclusions, the ACR decided not to pursue their own study.[41]

In June 1989, the ACR voted to accept the findings of the Katayama study, which in essence concluded that, from a strictly medical perspective, there is no scientific reason to justify any patient receiving ionic contrast media. However, the ACR stopped short of recommending universal use of LOCM but instead upheld the perogative of the individual radiologist to make the decision as to which contrast media was appropriate for each patient. Recognizing that cost and the lack of reimbursement for LOCM was a significant factor for physicians in making this choice, the ACR adopted a policy to actively pursue universal reimbursement by third-party payors for LOCM agents in the performance of radiologic exams.[41]

Summary

The broader use of LOCM in the United States will add significantly to the cost of providing health care. On a societal level, money spent on LOCM is not available to support other competing health care needs. On an institutional or radiology

department level, monies that are invested in the purchase of LOCM are not available to support other services and functions. According to Jacobson and Rosenquist, the added expense represented by yearly LOCM costs may mean that a radiology department may have to choose between that purchase and adding staff or purchasing computed tomographic, MRI scanners, or other technologies. Given limited budgets, radiology departments and hospital administrators will have to make the difficult determination of how to best allocate resources to maximize the quality of care provided to patients consistent with institutional goals.

Currently, reimbursement policies are playing a major role in limiting the use of LOCM. Although some United States hospitals have adopted universal use of LOCM, most use a combination of HOCM and LOCM products. If reimbursement for LOCM improves significantly, diffusion will occur rapidly since the effectiveness and increased safety of these agents is well recognized and the economic impact of LOCM will be absorbed by third-party payors.

Both HOCM and LOCM agents yield diagnostic images of comparable quality, however, LOCM are characterized by lower rates of adverse patient reactions. Reactions to contrast media, although rare, range from mild to very severe reactions including death. Currently about 10 million intravascular contrast injections are performed annually in the United States. However, the newer LOCM are approximately 10 times more expensive than the more widely used HOCM and the added cost of LOCM is currently not covered by many health insurance policies. Because the additional cost of LOCM often represents an uncompensated expense to hospitals and radiology departments, many facilities have policies limiting the use of LOCM to patients thought to be at highest risk of an adverse reaction to HOCM. These policies raise issues of patient comfort and safety and professional liability — issues which underscore the need for physicians to more fully inform patients, health care administrators, and third-

party payors about the risks and costs associated with the use of HOCM and LOCM.

Guidelines for the use of HOCM and LOCM are needed. These guidelines should be flexible to allow radiologists to exercise their medical judgment in responding to the needs of their patients and technology advances. Consideration should also be given to local standards of practice, expertise in radiology, medicine, pharmacy and law, budgetary considerations, patient and providers mix, and local reimbursement policies. The welfare of all patients should be the overriding concern in developing contrast media usage guidelines. The AMA is interested in working with specialty societies to evaluate appropriate indications for the use of diagnostic imaging agents, developing model guidelines to assist radiologists and referring physicians in understanding the risks and costs that attend the choice of LOCM versus HOCM, and disseminating this information to the medical community. The AMA also is interested in working with state and local medical societies and specialty societies to monitor legal actions that may arise over the use of HOCM and LOCM and to advise physicians regarding the use of informed consent and other risk management practices.

Recommendations

The Councils recommend adoption of the following policy statement on the use of contrast media agents:

- Manufacturers should adopt just and appropriate pricing policies for LOCM.
- Third-party payors should provide full reimbursement for the use of the contrast media which is deemed medically necessary by the physician.
- Avoidance of waste in the use of contrast media should be encouraged.

- The development and implementation by hospitals of procedures and policies to help ensure that non-ionic contrast media are used only when necessary should be supported.

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APPENDIX F

SAFE MEDICAL DEVICES ACT OF 1990

Public Law 101-629 — Nov. 28, 1990
101st Congress

AN ACT

To amend the Federal Food, Drug, and Cosmetic Act to make improvements in the regulation of medical devices, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE AND REFERENCE TO ACT.

(a) SHORT TITLE. — This Act may be cited as the "Safe Medical Devices Act of 1990".

(b) REFERENCE. — Whenever in this Act (other than in section 19) an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act.

SECTION 2. USER REPORTS.

(a) REQUIREMENT. — Section 519 (21 U.S.C. 360i) is amended by redesignating subsection (b) as subsection (c) and by inserting after subsection (a) the following:

"User Reports

"(b)(1)(A) Whenever a device user facility receives or otherwise becomes aware of information that reasonably sug-

gests that there is a probability that a device has caused or contributed to the death of a patient of the facility, the facility shall, as soon as practicable but not later than 10 working days after becoming aware of the information, report the information to the Secretary and, if the identity of the manufacturer is known, to the manufacturer of the device. In the case of deaths, the Secretary may by regulation prescribe a shorter period for the reporting of such information.

"(B) Whenever a device user facility receives or otherwise becomes aware of information that reasonably suggests that there is a probability that a device has caused or contributed to the serious illness of, or serious injury to, a patient of the facility, the facility shall, as soon as practicable but not later than 10 working days after becoming aware of the information, report the information to the manufacturer of the device or to the Secretary if the identity of the manufacturer is not known.

"(C) Each device user facility shall submit to the Secretary on a semi-annual basis a summary of the reports made under subparagraphs (A) and (B). Such summary shall be submitted on January 1 and July 1 of each year. The summary shall be in such form and contain such information from such reports as the Secretary may require and shall include —

"(i) sufficient information to identify the facility which made the reports for which the summary is submitted.

"(ii) in the case of any product which was the subject of a report, the product name, serial number, and model number,

"(iii) the name and the address of the manufacturer of such device, and

"(iv) a brief description of the event reported to the manufacturer.

The Secretary may by regulation alter the frequency and timing of reports required by this subparagraph.

"(D) For purposes of subparagraphs (A), (B), and (C), a device user facility shall be treated as having received or otherwise become aware of information with respect to a device of that facility when medical personnel who are employed by or otherwise formally affiliated with the facility receive or otherwise become aware of information with respect to that device in the course of their duties.

"(2) The Secretary may not disclose the identity of a device user facility which makes a report under paragraph (1) except in connection with —

"(A) an action brought to enforce section 301(q).

"(B) a communication to a manufacturer of a device which is the subject of a report under paragraph (1), or

"(C) a disclosure required under subsection (a).

This paragraph does not prohibit the Secretary from disclosing the identity of a device user facility making a report under paragraph (1) or any information in such a report to employees of the Department of Health and Human Services, to the Department of Justice, or to the duly authorized committees and subcommittees of the Congress.

"(3) No report made under paragraph (1) by —

"(A) a device user facility,

"(B) an individual who is employed by or otherwise formally affiliated with such a facility, or

"(C) a physician who is not required to make such a report, shall be admissible into evidence or otherwise used in any civil action involving private parties unless the facility, individual, or physician who made the report had knowledge of the falsity of the information contained in the report.

"(4) A report made under paragraph (1) does not affect any obligation of a manufacturer who receives the report to file a report as required under subsection (a).

"(5) For purposes of this subsection:

"(A) The term 'device user facility' means a hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician's office. The Secretary may by regulation include an outpatient diagnostic facility which is not a physician's office in such term.

"(B) The Terms 'serious illness' and 'serious injury' mean illness or injury, respectively, that —

"(i) is life threatening,

"(ii) results in permanent impairment of a body function or permanent damage to a body structure, or

"(iii) necessitates immediate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.".

(b) REGULATIONS. — The Secretary of Health and Human Services shall promulgate regulations to implement section 519(b) of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a) (including a definition of the summary required by paragraph (1)(C) of such section) not later than 12 months after the date of enactment of this Act. In promulgating the regulations, the Secretary shall minimize the administrative burdens on device user facilities consistent with the need to assure adequate information.

(c) EFFECTIVE DATE. — Section 519(b) of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a), shall take effect —

(1) upon the effective date of regulations promulgated under subsection (b), or

(2) upon the expiration of 12 months from the date of the enactment of this Act,

whichever occurs first.

(d) EDUCATION AND INFORMATION. — During the 18-month period beginning on the date of the enactment of this Act, the Secretary of Health and Human Services shall inform device user facilities (as defined in section 519(b)(5)(A) of the Federal Food, Drug, and Cosmetic Act) and manufacturers and distributors of devices respecting the requirements of section 519(b) of such Act. Additionally, the Secretary, to the extent practicable, shall provide persons subject to the requirements of such section assistance in the form of publications regarding such requirements.

(e) STUDY. — Not more than 36 months after the date of the enactment of this Act, the Comptroller General of the United States shall conduct a study of —

(1) the compliance by device user facilities (as defined in section 519(b)(5)(A) of the Federal Food, Drug, and Cosmetic Act) with the requirements of section 519(b) of such Act,

(2) the actions taken by the manufacturers of devices in response to reports made to them under such section,

(3) the cost effectiveness of such requirements and their implementation, and

(4) any recommendations for improvements to such requirements.

The Comptroller General shall complete the study and submit a report on the study not later than 45 months from the date of the enactment of this Act. The report shall be submitted to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human

Resources of the Senate and to the Secretary of Health and Human Services.

(f) REPORT TO CONGRESS. — Not later than 36 months after the date of enactment of this Act, the Secretary of Health and Human Services shall prepare and submit to the appropriate committees of Congress a report that contains an evaluation of the requirements of section 519(b) of the Federal Food, Drug, and Cosmetic Act. In preparing the report, the Secretary shall consult with individuals and organizations with an interest in health care and consumer issues. At a minimum, the report shall contain —

(1) an evaluation of the safety benefits of the requirements,

(2) an evaluation of the burdens placed on the Food and Drug Administration and on device user facilities by the requirements,

(3) an evaluation of the cost-effectiveness of the requirements, and

(4) recommendations for legislative reform.

SECTION 3. REPORTS.

(a) DISTRIBUTOR REPORTS. —

(1) Section 519(a) (21 U.S.C. 360i (a)) is amended by striking out "and" at the end of paragraph (4), by striking out the period at the end of paragraph (5) and inserting in lieu thereof "; and", and by adding after paragraph (5) the following:

"(6) shall require distributors who submit such reports to submit copies of the reports to the manufacturer of the device for which the report was made.".

(2) Section 519(a)(6), as added by the amendment made by paragraph (1), shall take effect upon the effective date of final regulations under subsection (c).

(b) CERTIFICATION, DEVICE TRACKING. —

(1) Section 519 (21 U.S.C. 360i), as amended by section 2, is amended by adding at the end the following:

"Certification

"(d) Each manufacturer, importer, and distributor required to make reports under subsection (a) shall submit to the Secretary annually a statement certifying that —

"(1) the manufacturer, importer, or distributor did file a certain number of such reports, or

"(2) the manufacturer, importer, or distributor did not file any report under subsection (a).

"Device Tracking

"(e) Every person who registers under section 510 and is engaged in the manufacture of —

"(1) a device the failure of which would be reasonably likely to have serious adverse health consequences and which is (A) a permanently implantable device, or (B) a life sustaining or life supporting device used outside a device user facility, or

"(2) any other device which the Secretary may designate, shall adopt a method of device tracking.".

(2) Section 520(j) (21 U.S.C. 360j(j)) is amended by striking out "No" and inserting in lieu thereof "Except as provided in section 519(e), no".

(3) Section 519(e), as added by the amendment made by paragraph (1), shall take effect upon the effective date of final regulations under subsection (c).

(c) REGULATIONS. —

(1)(A) Not later than 9 months after the date of the enactment of this Act, the Secretary of Health and Human Services shall issue proposed regulations —

(i) to require distributors of devices to establish and maintain records and to make reports (including reports required by part 803 of title 21 of the Code of Federal Regulations) under section 519 (a)(6) of the Federal Food, Drug, and Cosmetic Act, and

(ii) to implement section 519(e) of such Act.

The Secretary may exempt from regulations described in clause (i) classes of distributors of class I and class II devices from whom reports are not necessary for the protection of the public health.

(B) regulations under subparagraph (A) shall —

(i) require appropriate methods for maintenance of records to ensure that patients who receive devices can be provided the notification required by such Act.

(ii) require that manufacturers adopt effective methods of tracking devices,

(iii) take into account the position of distributors in the device distribution process, and

(iv) include such other requirements as the Secretary deems necessary for the adoption of an effective user tracking program under section 519(e) of such Act.

(2) Not later than 18 months after the date of the enactment of this Act, the Secretary shall issue final regulations to implement sections 519(a)(6) and 519(e) of the Federal Food, Drug, and Cosmetic Act. If the Secretary does not promulgate such final regulations upon the expiration of such 18 months, the Congress finds that there is good cause for the proposed regulations to be consid-

ered as the final regulations without response to comment because the implementation of sections 519(a)(6) and 519(e) of such Act are essential to protect the health of patients who use such devices. Consequently, in such event, the proposed regulations issued under paragraph (1) shall become final regulations as of the expiration of such 18 months. There shall be promptly published in the Federal Register notice of the new status of the proposed regulations.

SECTION 4. SUBSTANTIAL EQUIVALENCE; CLASSIFICATION REVISION.

(a) SUBSTANTIAL EQUIVALENCE. — Section 513(f) (21 U.S.C. 360C(f)) is amended by adding at the end the following:

"(3) If a manufacturer reports to the Secretary under section 510(k) that a device is substantially equivalent to another device —

"(i) which the Secretary has classified as a class III device under subsection (b).

"(ii) which was introduced or delivered for introduction into interstate commerce for commercial distribution before December 1, 1990, and

"(iii) for which no final regulation requiring premarket approval has been promulgated under section 519(b),

the manufacturer shall certify to the Secretary that the manufacturer has conducted a reasonable search of all information known or otherwise available to the manufacturer respecting such other device and has included in the report under section 510(k) a summary of and a citation to all adverse safety and effectiveness data respecting such other device and respecting the device for which the 510(k) report is being made and which has not been submitted to the Secretary

under section 519. The Secretary may require the manufacturer to submit the adverse safety and effectiveness data described in the report.".

(b) REVISION OF CLASSIFICATION. —

(1) SECTION 515 (21 U.S.C. 360e) IS AMENDED BY ADDING AT THE END THE FOLLOWING:

"Revision

"(i)(1) Before December 1, 1995, the Secretary shall by order require manufacturers of devices, which were introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and which are subject to revision of classification under paragraph (2), to submit to the Secretary a summary of and citation to any information known or otherwise available to the manufacturer respecting such devices, including adverse safety or effectiveness information which has not been submitted under section 519. The Secretary may require the manufacturer to submit the adverse safety or effectiveness data for which a summary and citation were submitted, if such data are available to the manufacturer.

"(2) After the issuance of an order under paragraph (1) but before December 1, 1995, the Secretary shall publish a regulation in the Federal Register for each device —

"(A) which the Secretary has classified as a class III device, and

"(B) for which no final regulation has been promulgated under section 515(b),

revising the classification of the device so that the device is classified into class I or class II, unless the regulation requires the device to remain in class III. In determining whether to revise the classification of a device or to require a device to

remain in class III, the Secretary shall apply the criteria set forth in section 513(a). Before the publication of a regulation requiring a device to remain in class III or revising its classification, the Secretary shall publish a proposed regulation respecting the classification of a device under this paragraph and provide reasonable opportunity for the submission of comments on any such regulation. No regulation requiring a device to remain in class III or revising its classification may take effect before the expiration of 90 days from the date of its publication in the Federal Register as a proposed regulation.

"(3) The Secretary shall, as promptly as is reasonably achievable, but not later than 12 months after the effective date of the regulation requiring a device to remain in class III, establish a schedule for the promulgation of a section 515(b) regulation for each device which is subject to the regulation requiring the device to remain in class III.".

(2) Section 520(1) (21 U.S.C. 360j(1)) is amended by adding at the end the following:

"(5)(A) Before December 1, 1991, the Secretary shall by order require manufacturers of devices described in paragraph (1), which are subject to revision of classification under subparagraph (B), to submit to the Secretary a summary of and citation to any information known or otherwise available to the manufacturers respecting the devices, including adverse safety or effectiveness information which has not been submitted under section 519. The Secretary may require a manufacturer to submit the adverse safety or effectiveness data for which a summary and citation were submitted, if such data are available to the manufacturer.

"(B) Except as provided in subparagraph (C), after the issuance of an order under subparagraph (A) but before December 1, 1992, the Secretary shall publish a regulation in the Federal Register for each device which is classified in

class III under paragraph (1) revising the classification of the device so that the device is classified into class I or class II, unless the regulation requires the device to remain in class III. In determining whether to revise the classification of a device or to require a device to remain in class III, the Secretary shall apply the criteria set forth in section 513(a). Before the publication of a regulation requiring a device to remain in class III or revising its classification, the Secretary shall publish a proposed regulation respecting the classification of a device under this subparagraph and provide an opportunity for the submission of comments on any such regulation. No regulation under this subparagraph requiring a device to remain in class III or revising its classification may take effect before the expiration of 90 days from the date of the publication in the Federal Register of the proposed regulation.

"(C) The Secretary may by notice published in the Federal Register extend the period prescribed by subparagraph (B) for a device for an additional period not to exceed 1 year.".

(3)(A) Notwithstanding section 520(l)(5) of the Federal Food, Drug, and Cosmetic Act, the Secretary of Health and Human Services shall not retain any daily wear soft or daily wear nonhydrophilic plastic contact lens in class III under such Act unless the Secretary finds that it meets the criteria set forth in section 513(a)(1)(C) of such Act. The finding and the grounds for the finding shall be published in the Federal Register. For any such lens, the Secretary shall make the determination respecting reclassification required in section 520(l)(5)(B) of such Act within 24 months of the date of the enactment of this paragraph.

(B) The Secretary of Health and Human Services may by notice published in the Federal Register extend the two-year period prescribed by subparagraph (A) for a lens for an additional period not to exceed one year.

(C)(i) Before classifying a lens in class II pursuant to subparagraph (A), the Secretary of Health and Human Services shall pursuant to section 513(a)(1)(B) of such Act assure that appropriate regulatory safeguards are in effect which provide reasonable assurance of the safety and effectiveness of such lens, including clinical and preclinical data if deemed necessary by the Secretary.

(ii) Prior to classifying a lens in class I pursuant to subparagraph (A), the Secretary shall assure that appropriate regulatory safeguards are in effect which provide reasonable assurance of the safety and effectiveness of such lens, including clinical and preclinical data if deemed necessary by the Secretary.

(D) Notwithstanding section 520(l)(5) of such Act, if the Secretary of Health and Human Services has not made the finding and published the finding required by subparagraph (A) within 36 months of the date of the enactment of this subparagraph, the Secretary shall issue an order placing the lens in class II.

(E) Any person adversely affected by a final regulation under this paragraph revising the classification of a lens may challenge the revision of the classification of such lens only by filing a petition under section 513(e) for a classification change.

SECTION 5. CLASSIFICATION AND RECLASSIFICATION OF DEVICES.

(a) STANDARDS. —

(1) Section 513(a)(1)(A)(ii) (21 U.S.C. 360c(a)(1)(A)(ii)) is amended by striking out "or to establish a performance standard" and inserting in lieu thereof "or to establish special controls".

(2) Section 513(a)(1)(B) (21 U.S.C. 360c(a)(1)(B)) is amended to read as follows:

"(B) CLASS II, SPECIAL CONTROLS. — A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance. For a device that is purported or represented to be for a use in supporting or sustaining human life, the Secretary shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance.".

(3) Clause (i) of section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)) is amended to read as follows:

"(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and".

(b) CLASSIFICATION CHANGE. — Section 513(e) (21 U.S.C. 360c(e)) is amended by redesignating clauses (1) and (2) as clauses (A) and (B), respectively, and by inserting "(1)" and "(e)" and by adding at the end the following:

"(2) By regulation promulgated under paragraph (1), the Secretary may change the classification of a device from class III —

"(A) to class II if the Secretary determines that special controls would provide reasonable assurance of the safety and effectiveness of the device and that general controls would not provide reasonable assurance of the safety and effectiveness of the device, or

"(B) to class I if the Secretary determines that general controls would provide reasonable assurance of the safety and effectiveness of the device.".

(c) F.D.A. AUTHORITY TO INITIATE RECLASSIFICATION. —

(1) Section 513(f)(2)(A) (21 U.S.C. 360c(f)(2)(A)) is amended by striking out "The manufacturer" and inserting in lieu thereof "The Secretary may initiate the reclassification of a device classified into class III under paragraph (1) of this subsection or the manufacturer".

(2) Section 520(l)(2) (21 U.S.C. 360j(l)(2)) is amended by striking out "The manufacturer" and inserting in lieu thereof "The Secretary may initiate the reclassification of a device classified into class III under paragraph (1) of this subsection or the manufacturer".

(3) The heading for section 513(f) (21 U.S.C. 360c(f)) is amended by inserting "and Reclassification" before "of".

SECTION 6. ESTABLISHMENT OF PERFORMANCE STANDARDS.

(a) PROCEDURE. — Section 514 (21 U.S.C. 360d) is amended —

(1) in subsection (a), by amending the first sentence to read as follows: "The special controls required by sec-

tion 513(a)(1)(B) shall include performance standards for a class II device if the Secretary determines that a performance standard is necessary to provide reasonable assurance of the safety and effectiveness of the device.",

(2) by striking out subsections (b) through (f),

(3) by redesignating subsection (g) as subsection (b),

(4) in subsection (b) (as redesignated), by amending paragraphs (1) and (2) to read as follows:

"(1)(A) The Secretary shall publish in the Federal Register a notice of proposed rulemaking for the establishment, amendment, or revocation of any performance standard for a device.

"(B) A notice of proposed rulemaking for the establishment or amendment of a performance standard for a device shall —

"(i) set forth a finding with supporting justification that the performance standard is appropriate and necessary to provide reasonable assurance of the safety and effectiveness of the device,

"(ii) set forth proposed findings with respect to the risk of illness or injury that the performance standard is intended to reduce or eliminate,

"(iii) invite interested persons to submit to the Secretary, within 30 days of the publication of the notice, requests for changes in the classification of the device pursuant to section 513(e) based on new information relevant to the classification, and

"(iv) invite interested persons to submit an existing performance standard for the device, including a draft or proposed performance standard, for consideration by the Secretary.

"(C) A notice of proposed rulemaking for the revocation of a performance standard shall set forth a finding with supporting justification that the performance standard is no

longer necessary to provide reasonable assurance of the safety and effectiveness of a device.

"(D) The Secretary shall provide for a comment period of not less than 60 days.

"(2) If, after publication of a notice in accordance with paragraph (1), the Secretary receives a request for a change in the classification of the device, the Secretary shall, within 60 days of the publication of the notice, after consultation with the appropriate panel under section 513, either deny the request or give notice of an intent to initiate such change under section 513(e).".

(b) CONFORMING AMENDMENTS. —

(1) Section 514(b) (as redesignated by subsection (a)(3)) is amended —

(A) in paragraph (3)(A), by striking out "paragraph (2)" and inserting in lieu thereof "paragraph (1)", and

(B) in paragraph (4)(A), by striking out "paragraphs (2) and (3)(B)" and inserting in lieu thereof "paragraphs (1), (2), and (3)(B)".

(2) Section 520 (i) (21 U.S.C. 360j(i)) is amended by striking out "514(g)(5)(B)" and inserting in lieu thereof "514(b)(5)(B)".

SECTION 7. REPORTS OF REMOVALS AND CORRECTIONS.

Section 519 (21 U.S.C. 360i), as amended by sections 2 and 3, is amended by adding at the end the following:

"Reports of Removals and Corrections

"(f)(1) Except as provided in paragraph (2), the Secretary shall by regulation require a manufacturer, importer, or distributor of a device to report promptly to the Secretary any correction or removal of a device undertaken by such manu-

facturer, importer, or distributor if the removal or correction was undertaken —

"(A) to reduce a risk to health posed by the device, or

"(B) to remedy a violation of this Act caused by the device which may present a risk to health.

A manufacturer, importer, or distributor of a device who undertakes a correction or removal of a device which is not required to be reported under this paragraph shall keep a record of such correction or removal.

"(2) No report of the corrective action or removal of a device may be required under paragraph (1) if a report of the corrective action or removal is required and has been submitted under subsection (a).

"(3) For purposes of paragraphs (1) and (2), the terms 'correction' and 'removal' do not include routine servicing.".

SECTION 8. RECALL AUTHORITY.

Section 518 (21 U.S.C. 360h) is amended by adding at the end the following new subsection:

"*Recall Authority*

"(e)(1) If the Secretary finds that there is a reasonable probability that a device intended for human use would cause serious, adverse health consequences or death, the Secretary shall issue an order requiring the appropriate person (including the manufacturers, importers, distributors, or retailers of the device) —

"(A) to immediately cease distribution of such device, and

"(B) to immediately notify health professionals and device user facilities of the order and to instruct such professionals and facilities to cease use of such device.

The order shall provide the person subject to the order with an opportunity for an informal hearing, to be held not later than 10 days after the date of the issuance of the order, on the actions required by the order and on whether the order should be amended to require a recall of such device. If, after providing an opportunity for such a hearing, the Secretary determines that inadequate grounds exist to support the actions required by the order, the Secretary shall vacate the order.

"(2)(A) If, after providing an opportunity for an informal hearing under paragraph (1), the Secretary determines that the order should be amended to include a recall of the device with respect to which the order was issued, the Secretary shall, except as provided in subparagraphs (B) and (C), amend the order to require a recall. The Secretary shall specify a timetable in which the device recall will occur and shall require periodic reports to the Secretary describing the progress of the recall.

"(B) An amended order under subparagraph (A) —

"(i) shall —

"(I) not include recall of a device from individuals, and

"(II) not include recall of a device from device user facilities if the Secretary determines that the risk of recalling such device from the facilities presents a greater health risk than the health risk of not recalling the device from use, and

"(ii) shall provide for notice to individuals subject to the risks associated with the use of such device.

In providing the notice required by clause (ii), the Secretary may use the assistance of health professionals who prescribed or used such a device for individuals. If a significant number of such individuals cannot be identified, the Secretary shall notify such individuals pursuant to section 705(b).

"(3) The remedy provided by this subsection shall be in addition to remedies provided by subsections (a), (b), and (c).".

SECTION 9. TEMPORARY SUSPENSION OF APPROVAL OF APPLICATION.

(a) SUSPENSION. — Section 515(e) (21 U.S.C. 360e(e)) is amended —

(1) by adding at the end the following:

"(3) If, after providing an opportunity for an informal hearing, the Secretary determines there is reasonable probability that the continuation of distribution of a device under an approved application would cause serious, adverse health consequences or death, the Secretary shall by order temporarily suspend the approval of the application approved under this section. If the Secretary issues such an order, the Secretary shall proceed expeditiously under paragraph (1) to withdraw such application.", and

(2) in the subsection heading, by inserting "and Temporary Suspension" after "Withdrawal".

(b) CONFORMING AMENDMENT. — Section 501(f) (21 U.S.C. 351(f) is amended —

(1) in subparagraph (A)(ii)(II), by striking out "or withdrawn" and inserting in lieu thereof ", suspended, or withdrawn",

(2) in subparagraph (B)(ii), by striking out "which does not have such an application in effect" and inserting in lieu thereof "which has an application which has been suspended or is otherwise not in effect", and

(3) in subparagraph (C), by striking out "which does not have such an application in effect" and inserting in lieu thereof "which has an application which has been suspended or is otherwise not in effect".

SECTION 10. POSTMARKET SURVEILLANCE.

Subchapter A of chapter 5 is amended by inserting after section 521 (21 U.S.C. 360k) the following new section:

"POSTMARKET SURVEILLANCE

"SEC. 522. (a) IN GENERAL. —

"(1) REQUIRED SURVEILLANCE. — The Secretary shall require a manufacturer to conduct postmarket surveillance for any device of the manufacturer first introduced or delivered for introduction into interstate commerce after January 1, 1991, that —

"(A) is a permanent implant the failure of which may cause serious, adverse health consequences or death.

"(B) is intended for a use in supporting or sustaining human life, or

"(C) potentially presents a serious risk to human health.

"(2) DISCRETIONARY SURVEILLANCE. — The Secretary may require a manufacturer to conduct postmarket surveillance for a device of the manufacturer if the Secretary determines that postmarket surveillance of the device is necessary to protect the public health or to provide safety or effectiveness data for the device.

"(b) SURVEILLANCE APPROVAL. — Each manufacturer required to conduct a surveillance of a device under subsection (a) shall, within 30 days of the first introduction or delivery

for introduction of such device into interstate commerce submit, for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the receipt of such protocol, shall determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct such surveillance and if such protocol will result in collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device. The Secretary may not approve such a protocol until it has been reviewed by an appropriately qualified scientific and technical review committee established by the Secretary.".

SECTION 11. USE OF PREMARKET APPROVAL DATA.

Section 520 (21 U.S.C. 360j) is amended —

(1) in subsection (c) —

(A) by striking out "under section 513 from class III to class II" and inserting in lieu thereof "from class III to class II or class I", and

(B) by inserting "(I) in accordance with subsection (h), and (2)" after "except", and

(2) in subsection (h) —

(A) in paragraph (3), by striking out "Any" and inserting in lieu thereof "Except as provided in paragraph (4), any", and

(B) by adding at the end the following new paragraph:

"(4)(A) Any information contained in an application for premarket approval filed with the Secretary pursuant to section 515(c), including clinical and preclinical tests or studies, but excluding descriptions of methods of manufacture and product composition, that demonstrates the safety and effectiveness of a device shall be available 1 year after the orig-

inal application for the fourth device of a kind has been approved by the Secretary, for use by the Secretary in approving devices, or determining whether a product development protocol has been completed, under section 515, establishing a performance standard under section 514, and reclassifying devices under subsections (e) and (f) of section 513, and subsection (l)(2). The Secretary shall deem devices that incorporate the same technologies, have the same principles of operation, and are intended for the same use or uses to be within a kind of device.

"(B) The Secretary, contemporaneously with the approval of the fourth device of a kind, shall publish an order in the Federal Register identifying the four devices of a kind that have been approved under section 515 and the date on which the data contained in premarket approval applications for the devices will be available to the Secretary for use, as described in subparagraph (A).

"(C) The publicly available detailed summaries of information respecting the safety and effectiveness of devices required by paragraph (1)(A) shall be available for use by the Secretary as the evidentiary basis for the regulatory action described in subparagraph (A).

"(D)(i) This paragraph shall become effective —

> "(I) on November 15, 1990, for devices for which four devices of a kind were approved on or before December 31, 1987, and
>
> "(II) on November 15, 1991, for devices not described in subclause (I).

"(ii) For each device described in clause (i)(I), the Secretary shall publish a notice in the Federal Register setting forth the date, which shall be not earlier than 1 year after the date of the notice, that data identified in subpararaph (A) shall be available for the use of the Secretary.

"(E)(i) Except as provided in clause (ii), the approval date of a device, for purposes of this paragraph, shall be the date of the letter of the Secretary to the applicant approving a device under section 515 and permitting the applicant to commercially distribute the device.

"(ii) For each device described in subparagraph (D)(i)(II) for which the original application for a fourth device of a kind is approved by the Secretary before November 1, 1991, the approval date of the fourth device of a kind shall be deemed to be November 15, 1991.

"(F) Any challenge to an order under subparagraph (B) shall be made not later than 30 days after the date of the Federal Register notice referred to in such subparagraph.".

SECTION 12. SUBSTANTIAL EQUIVALENCE.

(a) SUBSTANTIAL EQUIVALENCE. — Section 513 (21 U.S.C. 369j) is amended by adding at the end the following new subsection:

"*Substantial Equivalence*

"(i)(1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term 'substantially equivalent' or 'substantial equivalence' means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device —

"(i) has the same technological characteristics as the predicate device, or

"(ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including clinical data if deemed necessary by the Sec-

retary, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and efficacy than the predicate device.

"(B) For purposes of subparagraph (A), the term 'different technological characteristics' means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

"(2) A device may not be found to be substantially equivalent to a predicate device that has been removed from the market at the initiative of the Secretary or that has been determined to be misbranded or adulterated by a judicial order.

"(3)(A) As part of a submission under section 510(k) respecting a device, the person required to file a premarket notification under such section shall provide an adequate summary of any information respecting safety and effectiveness or state that such information will be made available upon request by any person.

"(B) Any summary under subparagraph (A) respecting a device shall contain detailed information regarding data concerning adverse health effects and shall be made available to the public by the Secretary within 30 days of the issuance of a determination that such device is substantially equivalent to another device.".

(b) REGULATIONS. — Within 12 months of the date of the enactment of this Act, the Secretary of Health and Human Services shall issue regulations establishing the requirements of the summaries under section 513(i)(3) of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a).

SECTION 13. JUDICIAL REVIEW.

Section 517(a) (21 U.S.C. 360g(a)) is amended —

(1) by striking out "or" at the end of paragraph (6), and

(2) by inserting after paragraph (7) the following new paragraphs:

"(8) an order pursuant to section 513(i),

"(9) a regulation under section 515(i)(2) or 520(l)(5)(B), or

"(10) an order under section 520(c)(4)(B),".

SECTION 14. HUMANITARIAN DEVICE EXEMPTION.

(a) EXEMPTION. — Section 520 (21 U.S.C. 360j) is amended by adding at the end the following:

"*Humanitarian Device Exemption*

"(m)(1) To the extent consistent with the protection of the public health and safety and with ethical standards, it is the purpose of this subsection to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.

"(2) The Secretary may grant a request for an exemption from the effectiveness requirements of sections 514 and 515 for a device for which the Secretary finds that —

"(A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States,

"(B) the device would not be available to a person with a disease or condition referred to in subparagraph (A) unless the Secretary grants such an exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition, and

"(C) the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

"(3) No person granted an exemption under paragraph (2) with respect to a device may sell the device for an amount that exceeds the costs of research and development, fabrication, and distribution of the device.

"(4) Devices granted an exemption under paragraph (2) may only be used —

"(A) in facilities that have established, in accordance with regulations of the Secretary, a local institutional review committee to supervise clinical testing of devices in the facilities, and

"(B) if, before the use of a device, an institutional review committee approves the use in the treatment or diagnosis of a disease or condition referred to in paragraph (2)(A).

"(5) An exemption under paragraph (2) shall be for a term of 18 months and may only be initially granted in the 5-year period beginning on the date regulations under paragraph (6) take effect. The Secretary may extend such an exemption for a period of 18 months if the Secretary is able to make the findings set forth in paragraph (2) and if the applicant supplies information demonstrating compliance with paragraph (3). An exemption may be extended more than once and may be extended after the expiration of such 5-year period.

"(6) Within one year of the date of the enactment of this subsection, the Secretary shall issue regulations to implement this subsection.".

(b) EFFECTIVE DATE. — Subsection (m) of section 520 of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a), shall take effect on the effective date of the regulations issued by the Secretary under paragraph (6) of such subsection.

(c) REPORT. — Within 4 years after the issuance of regulations under section 520(m)(6) of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a), the Secretary of Health and Human Services shall report to the Congress (1) on the types of devices exempted under such section, (2) an evaluation of the effects of such section, and (3) a recommendation on extension of the section.

SECTION 15. ESTABLISHMENT OF THE OFFICE OF INTERNATIONAL RELATIONS.

(a) OFFICE. — Title VIII is amended by adding at the end the following:

"OFFICE OF INTERNATIONAL RELATIONS

"SEC. 803. (a) There is established in the Department of Health and Human Services an Office of International Relations.

"(b) In carrying out the functions of the office under subsection (a), the Secretary may enter into agreements with foreign countries to facilitate commerce in devices between the United States and such countries consistent with the requirements of this Act. In such agreements, the Secretary shall encourage the mutual recognition of —

"(1) good manufacturing practice regulations promulgated under section 520(f), and

"(2) other regulations and testing protocols as the Secretary determines to be appropriate."

(b) REPORT. — Not later than 2 years after the date of the enactment of this Act, the Secretary of Health and Human Services shall prepare and submit to the appropriate committees of Congress a report on the activities of the Office of International Relations under section 803 of the Federal Food, Drug, and Cosmetic Act, added by subsection (a).

SECTION 16. REVIEW OF MARKET APPLICATIONS FOR ARTICLES COMPRISING COMBINATIONS OF DRUGS, DEVICES, AND BIOLOGICS.

(a) REVIEW. — Section 503 (21 U.S.C. 353) is amended —

(1) by striking out the section heading and inserting in lieu thereof the following:

"EXEMPTIONS AND CONSIDERATION FOR CERTAIN DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS",

and

(2) by adding at the end the following:

"(f)(1) The Secretary shall designate a component of the Food and Drug Administration to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of actions is that of —

"(A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction,

"(B) a device, the persons charged with premarket review of devices shall have primary jurisdiction, or

"(C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.

"(2) Nothing in this subsection shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article.

"(3) The Secretary shall promulgate regulations to implement market approval procedures in accordance with paragraphs (1) and (2) not later than 1 year after the date of enactment of this subsection.

"(4) As used in this subsection:

"(A) The term 'biological product' has the meaning given the term in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

"(B) The term 'market clearance' includes —

"(i) approval of an application under section 505, 507, 515, or 520(g),

"(ii) a finding of substantial equivalence under this subchapter, and

"(iii) approval of a product or establishment license under subsection (a) or (d) of section 351 of the Public Health Service Act (42 U.S.C. 262).".

(b) DEFINITIONS. — Section 201 (21 U.S.C. 321) is amended —

(1) in paragraph (g)(1), by striking out "; but does not include devices or their components, parts, or accessories", and

(2) in paragraph (h)(3), by striking out "any of its principal" and inserting in lieu thereof "its primary".

SECTION 17. CIVIL PENALTIES.

(a) AMENDMENT. — Section 303 (21 U.S.C. 333) is amended by adding at the end the following:

"(f)(1)(A) Except as provided in subparagraph (B), any person who violates a requirement of this Act which relates to devices shall be liable to the United States for a civil penalty in an amount not to exceed $15,000 for each such violation, and not to exceed $1,000,000 for all such violations adjudicated in a single proceeding.

"(B) Subparagraph (A) shall not apply —

"(i) to any person who violates the requirements of section 519(a) or 520(f) unless such violation constitutes (I) a significant or knowing departure from such requirements, or (II) a risk to public health.

"(ii) to any person who commits minor violations of section 519(e) or 519(f) (only with respect to correction reports) if such person demonstrates substantial compliance with such section, or

"(iii) to violations of section 501(a)(2)(A) which involve one or more devices which are not defective.

"(2)(A) A civil penalty under paragraph (1) shall be assessed by the Secretary by an order made on the record after opportunity for a hearing provided in accordance with this subparagraph and section 554 of title 5, United States Code. Before issuing such an order, the Secretary shall give written notice to the person to be assessed a civil penalty under such order of the Secretary's proposal to issue such order and provide such person an opportunity for a hearing on the order. In the course of any investigation, the Secretary may issue subpoenas requiring the attendance and testimony of witnesses and the production of evidence that relates to the matter under investigation.

"(B) In determining the amount of a civil penalty, the Secretary shall take into account the nature, circumstances, extent, and gravity of the violation or violations and, with respect to the violator, ability to pay, effect on ability to continue to do business, any history of prior such violations,

the degree of culpability, and such other matters as justice may require.

"(C) The Secretary may compromise, modify, or remit, with or without conditions, any civil penalty which may be assessed under paragraph (1). The amount of such penalty, when finally determined, or the amount agreed upon in compromise, may be deducted from any sums owing by the United States to the person charged.

"(3) Any person who requested, in accordance with paragraph (2)(A), a hearing respecting the assessment of a civil penalty and who is aggrieved by an order assessing a civil penalty may file a petition for judicial review of such order with the United States Court of Appeals for the District of Columbia Circuit or for any other circuit in which such person resides or transacts business. Such a petition may only be filed within the 60-day period beginning on the date the order making such assessment was issued.

"(4) If any person fails to pay an assessment of a civil penalty —

> "(A) after the order making the assessment becomes final, and if such person does not file a petition for judicial review of the order in accordance with paragraph (3), or
>
> "(B) after a court in an action brought under paragraph (3) has entered a final judgment in favor of the Secretary,

the Attorney General shall recover the amount assessed (plus interest at currently prevailing rates from the date of the expiration of the 60-day period referred to in paragraph (3) or the date of such final judgment, as the case may be) in an action brought in any appropriate district court of the United States. In such an action, the validity, amount, and appropriateness of such penalty shall not be subject to review.".

(b) EFFECTIVE DATE OF APPLICATION TO DEVICE USER FACILITIES. —

(1) The Secretary of Health and Human Services shall conduct a study to determine whether there has been substantial compliance with the requirements of section 519(b) of the Federal Food, Drug, and Cosmetic Act by device user facilities (as defined in section 519(b)(5)(A) of such Act). The Secretary shall report the results of the study to the Congress after the expiration of 45 months after the date of the enactment of this Act.

(2)(A) If upon the expiration of 48 months after the date of the enactment of this Act the Secretary has not made the report required by paragraph (1), section 303(f) of the Federal Food, Drug, and Cosmetic Act, as added by the amendment made by subsection (a), shall take effect with respect to device user facilities (as defined in section 519(b)(5)(A) of such Act).

(B) If in the report under paragraph (1) the Secretary reports that there has been substantial compliance with the requirements of such section 519(b) by a type of device user facility and if the Secretary does not make a determination under subparagraph (C) with respect to such type of facility, such section 303(f) shall not take effect with respect to such type of facility.

(C) If the Secretary determines in the report under paragraph (1) that there is not substantial compliance with the requirements of such section 519(b) by a type of device user facility or if the Secretary makes such a determination after making the report under paragraph (1), such section 303(f) shall take effect with respect to such type of facility upon the effective date of the report.

SECTION 18. MISCELLANEOUS.

(a) SECTION 513(f). — Section 513(f)(2) (21 U.S.C. 360c (f)(2) is amended in subparagraph (B)(i), by striking out

"the Secretary shall" and inserting in lieu thereof "the Secretary may for good cause shown".

(b) SECTION 514. — Section 514(b) (21 U.S.C. 360d(b)(4)(B)) (as so redesignated) is amended —

> (1) in paragraph (3)(B) (as so redesignated), by striking out ", after affording all interested persons an opportunity for an informal hearing,", and
>
> (2) in clause (ii) of paragraph (4)(A) (as so redesignated), by striking out "unless" and all that follows in that clause and inserting in lieu thereof the following: "which demonstrates good cause for referral and which is made before the expiration of the period for submission of comments on such proposed regulation refer such proposed regulation,".

(c) SECTION 515. — Section 515(c)(2) (21 U.S.C. 360e(c)(2)) is amended by striking out "paragraph (1), the Secretary shall refer such application" and inserting in lieu thereof "paragraph (1), the Secretary —

> "(A) may on the Secretary's own initiative refer such application, or
>
> "(B) shall, upon the request of an applicant unless the Secretary finds that the information in the application which would be reviewed by a panel substantially duplicates information which has previously been reviewed by a panel appointed under section 513,

refer such application".

(d) SECTION 516. — Section 516(a) (21 U.S.C. 360f(a)), is amended (1) by striking out "and after consultation with the appropriate panel or panels under section 513", and (2) by striking out the last sentence.

(e) SECTION 520(f). — Section 520(f)(1)(A) (21 U.S.C. 360j(f)(1)(A) is amended by inserting "pre-production design

validation (including a process to assess the performance of a device but not including an evaluation of the safety or effectiveness of a device)," after "manufacture,".

(f) SECTION 520(l). — Section 520(l)(2) (21 U.S.C. 360j (1)(2)) is amended by striking out "and after affording the petitioner an opportunity for an informal hearing".

SECTION 19. ELECTRONIC PRODUCTS.

(a) IN GENERAL. —

(1) Subpart 3 of part F of title III of the Public Health Service Act is amended as follows:

(A) The heading for the subpart is amended to read as follows:

"SUBCHAPTER C — ELECTRONIC PRODUCT RADIATION CONTROL".

(B) The subpart is amended by striking out "subpart" each place it occurs and inserting in lieu thereof "subchapter".

(2)(A) Section 356 of such Act is amended —

(i) by striking out "358" each place it occurs and inserting in lieu thereof "534", and

(ii) by striking out "sections 3648 and 3709 of the Revised Statutes of the United States (31 U.S.C. 529, 41 U.S.C. 5)" and inserting in lieu thereof "section 3324 of title 31, United States Code, and section 3709 of the Revised Statutes of the United States (41 U.S.C. 5)".

(B) Section 358(a)(1)(E) of such Act is amended by striking out "355" and inserting in lieu thereof "531".

(C) Section 359 of such Act is amended —

(i) by striking out "358" each place it occurs and inserting in lieu thereof "534", and

(ii) by striking out "360A" each place it occurs and inserting in lieu thereof "537".

(D) Section 360 of such Act is amended by striking out "358" each place it occurs and inserting in lieu thereof "534".

(E) Section 360A of such Act is amended —

(i) by striking out "358" and inserting in lieu thereof "534", and

(ii) by striking out "359" each place it occurs and inserting in lieu thereof "535".

(F) Section 360B of such Act is amended —

(i) by striking out "358" each place it occurs and inserting in lieu thereof "534",

(ii) by striking out "359" each place it occurs and inserting in lieu thereof "535", and

(iii) by striking out "360A" each place it occurs and inserting in lieu thereof "537".

(G) Section 360C of such Act is amended —

(i) by striking out "358" and inserting in lieu thereof "534",

(ii) by striking out "360B" each place it occurs and inserting in lieu thereof "538", and

(iii) by striking out "360F" and inserting in lieu thereof "542".

(H) Section 360F of such Act is amended by striking out "358" and inserting in lieu thereof "534".

(3) Section 354 of such Act is repealed and sections 355 through 360F of such Act are redesignated as sections 531 through 542, respectively.

(4) Subpart 3 of part F of title III of the Public Health Service Act, as amended by paragraphs (1) and (2) of this subsection, is transferred to chapter V of the Federal Food, Drug, and Cosmetic Act and is placed after section 528 and sections 354 through 360F of such subpart are redesignated as sections 530 through 542 of the Federal Food, Drug, and Cosmetic Act, respectively.

(b) CONFORMING AMENDMENT. — The heading for part F of title III of the Public Health Service Act is amended by striking out "AND CONTROL OF RADIATION".

(C) CONSTRUCTION. — The transfer of subpart 3 of part F of title III of the Public Health Service Act to the Federal Food, Drug, and Cosmetic Act does not change the application of the requirements of such subpart and such Act to electronic products which were in effect on the date of the enactment of this Act.

Approved November 28, 1990.

APPENDIX G

15 USCS § 1261 (1992)

3. (g) The term "toxic" shall apply to any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface.

(h)(1) The term "highly toxic" means any substance which falls within any of the following categories: (a) Produces death within fourteen days in half or more than half of a group of ten or more laboratory white rats each weighing between two hundred and three hundred grams, at a single dose of fifty milligrams or less per kilogram of body weight, when orally administered; or (b) produces death within fourteen days in half or more than half of a group of ten or more laboratory white rats each weighing between two hundred and three hundred grams, when inhaled continuously for a period of one hour or less at an atmospheric concentration of two hundred parts per million by volume or less of gas or vapor or two milligrams per liter by volume or less of mist or dust, provided such concentration is likely to be encountered by man when the substance is used in any reasonable foreseeable manner; or (c) produces death within fourteen days in half or more than half of a group of ten or more rabbits tested in a dosage of two hundred milligrams or less per kilogram of body weight, when administered by continuous contact with the bare skin for twenty-four hours or less.

(2) If the Secretary finds that available data on human experience with any substance indicate results different from those obtained on animals in the above-named dosages or concentrations, the human data shall take precedence.

(1)(A) Except as provided in paragraphs (2) and (3), if a hazardous substance or its packaging is subject to a cautionary labeling requirement under section 2(p) or 3(b) [15 USCS §§1261(p), 1262(b)] designed to protect against a risk of ill-

ness or injury associated with the substance, no State or political subdivision of a State may establish or continue in effect a cautionary labeling requirement applicable to such substance or packaging and designed to protect against the same risk of illness or injury unless such cautionary labeling requirement is identical to the labeling requirement under section 2(p) or 3(b) [15 USCS §§ 1261(p), 1262(b)].

"(B) Except as provided in paragraphs (2), (3), and (4), if under regulations of the Commission promulgated under or for the enforcement of section 2(q) [15 USCS § 1261(q)] a requirement is established to protect against a risk of illness or injury associated with a hazardous substance, no State or political subdivision of a State may establish or continue in effect a requirement applicable to such substance and designed to protect against the same risk of illness or injury unless such requirement is identical to the requirement established under such regulations.

"(2) The Federal Government and the government of any State or political subdivision of a State may establish and continue in effect a requirement applicable to a hazardous substance for its own use (or to the packaging of such a substance) which requirement is designed to protect against a risk of illness or injury associated with such substance and which is not identical to a requirement described in paragraph (1) applicable to such substance (or packaging) and designed to protect against the same risk of illness or injury if the Federal, State, or political subdivision requirement provides a higher degree of protection from such risk of illness or injury than the requirement described in paragraph (1).

TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT

DEFINITIONS

21 USCS § 321 (1992)

§ 321. Definitions; generally

(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A Food for which a claim, subject to sections 403r(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D) [21 USCS § 343(r)(1)(B), (3) or (r)(1)(B), (5)(D)], is made in accordance with the requirements of section 403(r) [21 USCS § 343(r)] is not a drug under clause (B) solely because the label or labeling contains such a claim.

(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c) [21 USCS §§ 331(i), 343(f), 352(c), 362(c)]) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is —

(1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appearing on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(m) The term "labeling" means all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the articles to which the labeling or advertising related under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

(p) The term "new drug" means —

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience

to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act [enacted June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

(bb) The term "abbreviated drug application" means an application submitted under section 505(j) or 507 [21 USCS § 355(j) or 357] for the approval of a drug that relies on the approved application of another drug with the same active ingredient to establish safety and efficacy, and —

(1) in the case of section 306 [21 USCS § 335a], includes a supplement to such an application for a different or additional use of the drug but does not include a supplement to such an application for other than a different or additional use of the drug, and

(cc) The term "knowingly" or "knew" means that a person, with respect to information —

(1) has actual knowledge of the information, or

(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT
DRUGS AND DEVICES

21 USCS § 353 (1992)

(B) *because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, or*

(C) *is limited by an approved application under section 505 [21 USCS § 355] to use under the professional supervision of a practitioner licensed by law to administer such drug, [;]*

shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.

(3) The Administrator may by regulation remove drugs subject to section 502(d) [21 USCS § 352(d)] and section 505 [21 USCS § 355] from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health.

(4) A drug which is subject to paragraph (1) of this subsection shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement "Caution: Federal law prohibits dispensing without prescription." A drug to which paragraph (1) of this subsection does not apply

shall be deemed to be misbranded if at any time prior to dispensing its label bears the caution statement quoted in the preceding sentence.

(g) Regulations.

(1) The Secretary shall designate a component of the Food and Drug Administration to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of —

(A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction,

(B) a device, the persons charged with premarket review of devices shall have primary jurisdiction, or

(C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.

(2) Nothing in this subsection shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article.

TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUGS, AND COSMETIC ACT
ELECTRONIC PRODUCT RADIATION CONTROL

21 USCS § 360hh (1992)

§ 360hh. Definitions

(2) the term "electronic product" means (A) any manufactured or assembled product which, when in operation, (i) contains or acts as part of an electronic circuit and (ii) emits (or in the absence of effective shielding or other controls would emit) electronic product radiation, or (B) any manufactured or assembled article which is intended for use as a component, part, or accessory of a product described in clause (A) and which when in operation emits (or in the absence of effective shielding or other controls would emit) such radiation;

(3) the term "manufacturer" means any person engaged in the business of manufacturing, assembling, or importing of electronic products;

(4) the term "commerce" means (A) commerce between any place in any State and any place outside thereof; and (B) commerce wholly within the District of Columbia; and

(5) the term "State" includes the District of Columbia, the Commonwealth of Puerto Rico, the Northern Mariana Islands, the Virgin Islands, Guam, and American Samoa.

§ 360j

(a) Restricted devices

(1) The Secretary may by regulation require that a device be restricted to sale, distribution, or use—

(A) only upon the written or oral authorization of a practitioner licensed by law to administer or use such device, or

(B) upon such other conditions as the Secretary may prescribe in such regulation,

if, because of its potentiality for harmful effect or the collateral measures necessary to its use, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness. No condition prescribed under subparagraph (B) may restrict the use of a device to persons with specific training or experience in its use or to persons for use in certain facilities unless the Secretary determines that such a restriction is required for the safe and effective use of the device. No such condition may exclude a person from using a device solely because the person does not have the training or experience to make him eligible for certification by a certifying board recognized by the American Board of Medical Specialties or has not been certified by such a Board. A device subject to a regulation under this subsection is a restricted device.

(2) The label of a restricted device shall bear such appropriate statements of the restrictions required by a regulation under paragraph (I) as the Secretary may in such regulation prescribe.

TITLE 31. CIVIL CODE
SUBTITLE 4. OBLIGATIONS AND CONTRACTS
PART I. OBLIGATIONS
CHAPTER 243. NATURE AND EFFECTS OF OBLIGATIONS

31 L.P.R.A. § 3018 (1990)

§ 3018. Fraud, negligence, or delay in fulfilling obligation

Those who in fulfilling their obligations are guilty of fraud, negligence, or delay, and those who in any manner whatsoever act in contravention of the stipulations of the same, shall be subject to indemnify for the losses and damages caused thereby.

APPENDIX H

LETTERHEAD —
DEPARTMENT OF HEALTH & HUMAN SERVICES

October 27, 1992

In reply refer to file F92-34723

Jose Otero
213 Pres. Ramirez Street
Hato, Puerto Rico 00918

Dear Mr. Otero:

This is in reply to your letter of October 10, 1992, concerning your request for a copy of the approval letter for Conray 60.

Enclosed are the documents you have requested.

This concludes your request.

If there are any problems with this response, please notify us *in writing* of your specific problem(s). Please reference the above file number.

Sincerely yours,

s/ KATHRYN E. ELLSWORTH

KATHRYN E. ELLSWORTH
Freedom of Information
Officer
Center for Drug Evaluation
and Research, HFD-19

May 23, 1962

Mallinckrodt Chemical Works
Attention: Dr. Floyd P. Hallett
Second and Mallinckrodt Streets
St. Louis 7, Missouri

Gentlemen:

Reference is made to your new drug application dated December 29, 1961, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "Conray."

We also acknowledge receipt of your additional communication dated March 29, 1962.

In accord with the provisions of regulation 130.4(d) the application was conditionally filed on March 30, 1962.

In accord with the provisions of regulation 130.4(d) the application is now conditionally effective and as provided in section 130.10 of the regulations will be effective when you submit specimens of final printed labeling for the drug identical in content to the draft copy. If the new drug is marketed prior to the submission to the Division of New Drugs of specimens of such labeling, the application will be considered incomplete under section 505(b)(6) of the Act, now filed as an application provided for in section 505(b), and not effective.

We recommend that you give consideration to the provisions of section 502(c) of the Act by designing the printed labeling to bear information required by the Act prominently and conspicuously as compared to other words, statements, designs, and devices; and to those of section 301(I) which prohibits the use in the labeling or in any advertising of any representation or suggestion that an application with respect to the drug is effective under section 505, or that the drug complies with the provisions of this section.

Paragraph (9) of the new drug application form is regarded as a commitmemt on your part that all representations in this application regarding the components, composition, manufacturing methods, facilities, controls, and labeling apply to the drug produced until an effective supplement provides for a change or the article is no longer a new drug.

Section 505(e) of the Act provides for the suspension of the effectiveness of the application if further experience and tests with the article show it to be unsafe for use or if it is found that the application contains any untrue statement of a material fact. The application may contain an untrue statement of a material fact by reason of any labeling or advertising in which you prescribe, recommend or suggest conditions of use of the drug differing by reason of omissions or otherwise from the conditions of use provided for in the application.

The effectiveness of this application does not extend to the drug labeled with another distributor's name, or repacked, or relabeled by another person, unless covered by an effective original or supplemental application.

The effectiveness of this application under section 505 in no way relieves you of the responsibility for complying with all other provisions of the Act.

Please submit five copies of the final printed labels and other labeling and four finished market packages of the drug when available.

Sincerely yours,

s/ EFM

EMMETT F. MADIGAN, M.D.
Medical Officer
Division of New Drugs
Bureau of Medicine

cc: SL (w/dup. NDA)
ND
BM RWJennings:vrb:A
5-18-62
Orig. Cond. Eff.

LETTERHEAD —

MALLINCKRODT CHEMICAL WORKS

August 13, 1962

Division of New Drugs
Bureau of Medicine
Department of Health, Education and Welfare
Washington 25, D.C.

NDA 13-295

Gentlemen:

In a letter dated May 23, 1962, from Emmett P. Madigan, M.D., Medical Officer, we were advised that our NDA 13-295 on CONRAY* was conditionally effective and would become effective upon submission of final printed labeling identical in content to the draft copy. Enclosed are five copies each of the labels and other labeling for CONRAY. This includes (1) the label which is directly printed on the 20 and 30 ml vial and 30 ml ampul; (2) the individual box, on which the label is printed directly, for the 20 and 30 ml vial and 30 ml ampul; (3) the label for the 25 unit packages of 20 and 30 ml vials and 30 ml ampuls and (4) the package insert which will be included in the individual and 25 unit packages of CONRAY.

A representative sample of the finished market packages and new drug substance, pursuant to Part 5(a) ii of the NDA, will be forwarded under separate cover within the next few days.

Sincerely yours,

s/ FLOYD P. HALLETT, PH. D.

FLOYD P. HALLETT, PH. D.
Director

FPH:ck
*Trademark
Encs.

NDA 13-295 CONRAY

Five copies of the label for direct printing on the 20 ml vial

0953 Sterile Solution 20 ml
CONRAY
BRAND OF
MEGLUMINE IOTHALAMATE 60%
FOR INTRAVENOUS UROGRAPHY
CAUTION: Federal law prohibits
dispensing without prescription.
USUAL DOSAGE: SEE PACKAGE INSERT.
PROTECT FROM LIGHT
MALLINCKRODT PHARMACEUTICALS
Mallinckrodt Chemical Works
6-62 St. Louis, Missouri

CONRAY
BRAND OF MEGLUMINE IOTHALAMATE 60%
FOR
INTRAVENOUS UROGRAPHY

DESCRIPTION

CONRAY is an x-ray contrast medium for intravenous urography developed by Mallinckrodt research. It is a sterile aqueous solution containing 60% w/v of the N-methylglucamine salt of 5-acetamido-2,4,6-trilodo-N-methylisophthalamic acid. Each milliliter of CONRAY contains 0.6 Gm. meglumine iothalamate, not more than 0.11 mg. calcium disodium ethylenediaminetetra-acetate as a stabilizer and not more than 0.15 mg. of sodium biphosphate as a buffer. The free acid contains 62% iodine and the 60% solution provides 28.2% iodine (282 mg./ml.).

Following intravenous injection, CONRAY is rapidly excreted by the kidneys. Maximum radiographic density in the kidney calyces and pelves occurs in most instances about 3-8 minutes after injection.

Aqueous solutions of CONRAY are sensitive to light and must be protected from strong daylight or direct exposure to the sun. Crystallization of CONRAY at normal storage temperatures and even below 32° F. does not occur.

DIRECTIONS FOR USE

Patient Preparation

Appropriate preparation of the patient is suggested for optimum results. A low residue diet is recommended for the day preceding the examination. The patient should be directed to abstain from fluids 12 to 15 hours before the administration of CONRAY, and unless contraindicated, a laxative is given the evening before the examination.

Dosage

Adult: The usual adult dose of CONRAY is 25-30 ml. Children 14 years of age and over, of average weight, may receive the adult dose. The total dose is normally injected within 30-90 seconds.

Children: The dosage for children is reduced in proportion to age and body weight. The following approximate schedule is recommended for infants and children based on a dosage of about 0.5 ml. per kilogram of body weight.

Under 6 months of age	5 ml.
6-12 months	8 ml.
1-2 years	10 ml.
2-5 years	12 ml.
5-8 years	15 ml.
8-12 years	18 ml.
12-14 years	20-30 ml.

Radiography

A preliminary radiograph of the abdomen is suggested before the injection is made. In normal kidneys, CONRAY appears in the urine almost immediately after injection. Generally, maximum radiographic density occurs in about 3-8 minutes. However, it is advisable to make additional exposures at 10 and 15 minutes to compensate for individual variation. Whenever functional disturbances are present, additional films may be taken to determine a delayed appearance of the medium or complete absence of visualization.

SCREENING OF PATIENTS

Prior to injection of any contrast medium, the patient should be questioned to obtain a history of allergy. A posi-

tive history does not arbitrarily contraindicate the use of the agent, but rather points up the need for extra caution and for preparedness to treat any reaction to the injection.

Various means of sensitivity testing have been employed in an effort to detect potential reactions to contrast media. On this point, the N.N.D. 1962, page 541, states: "Since the causes of severe reactions are unknown and preliminary testing is unreliable as an indication of which patients will react unfavorably, the only other safeguards are a physical examination and a careful evaluation of the patient's history to screen out subjects known to suffer from allergy or severe cardiovascular disease, plus the provision of facilities for resuscitation and the training of staff members in their prompt use if the need arises." Of the various sensitivity tests, the intravenous injection method has been employed most frequently. It is performed by injecting 1 or 2 ml. of the medium intravenously and observing the patient closely. Reaction to the medium may be evidenced by periorbital swelling, hives, respiratory difficulty, nausea and vomiting, drop in blood pressure, and signs of shock. If a reaction occurs, usually it will be noted within 5 to 10 minutes.

SIDE EFFECTS

Side effects associated with the use of CONRAY in intravenous urography have been minor and rather infrequently observed. Included among the minor reactions which may be encountered are nausea, vomiting, dizziness, and urticaria. In over 1,000 carefully studied cases of intravenous urography, approximately 90% of the patients receiving CONRAY experienced no untoward reactions.[1]

Since serious reactions have been reported with all previous iodinated intravascular contrast media, the possibility of such reactions to CONRAY cannot be ruled out. With regard to

[1] Data from private reports submitted to Mallinckrodt Pharmaceuticals.

iodinated contrast media in general, the N.N.D. 1962 states: "The severe reactions are of two general types: (1) Infrequently there may be severe respiratory difficulty with wheezing, bronchial spasm and sometimes laryngeal spasm, plus swelling of the lips and eyelids and giant urticaria. This is the so-called anaphylactic response and calls for the prompt administration of oxygen together with the intravenous injection of suitable antiallergic agents. (2) Somewhat more frequent is the so-called cardiovascular collapse, in which there is sudden drop in blood pressure, increase in pulse rate, dyspnea, confusion and cyanosis leading to unconsciousness, extreme pallor and the disappearance of the pulse at the wrist. Oxygen is employed as prompt as possible together with the injection of a suitable vasopressor agent."

Because of the possibility of a reaction to the contract medium, the patient should not be left alone for a period of approximately 15 minutes immediately following the injection.

Many institutions have established emergency kits or similar arrangements to facilitate prompt treatment at the first sign of a severe reaction. This kit commonly includes oxygen, diphenhydramine hydrochloride, penylephrine hydrochloride, metaraminol (Aramine-M.S.D.), hydrocortisone sodium succinate (Solu-Cortef Upjohn), a short acting barbiturate, physiological saline, and other emergency drugs. The standby drugs should be used according to the recognized procedures for treating severe reactions of this type. In the anoxic patient, the administration of epinephrine requires caution because it may induce ventricular fibrillation. Respiratory stimulation with metrazol, picrotoxin, and nikethamide is also contraindicated because of their possible convulsant action.

CONTRAINDICATIONS

Caution is required in any case involving severe systemic disease. In patients with advanced renal disease, CONRAY

should be used with caution and then only when the need for the examination dictates, since excretion of the medium may be severely impaired. Many clinicians feel that in patients exhibiting a positive reaction to the sensitivity test the medium is not absolutely contraindicated. Rather, in those cases in which the diagnostic information to be obtained makes the examination advisable, a positive reaction emphasizes the need for readily available facilities and drugs for emergency use.

PACKAGING

CONRAY is available in 20 and 30 ml. vials and 30 ml. ampuls in packages of 1 and 25.

Mallinckrodt
Pharmaceuticals
LINKING CHEMISTRY TO MEDICINE

Mallinckrodt Chemical Works
St. Louis 7, Missouri, U.S.A.
Pointe Claire (Montreal), Quebec, Canada

NDA 13-295

Feb. 8, 1963

Mallinckrodt Chemical Works
Attention: Dr. Floyd P. Hallett
Second and Mallinckrodt Streets
St. Louis 7, Missouri

Gentlemen:

We acknowledge the receipt on August 16, 1962 of your communication dated August 13, 1962 enclosing printed labeling pursuant to your new drug application for "Conray."

We also acknowledge the receipt of your communication dated August 31, 1962 and the samples described therein on September 7 and 5, 1962, respectively.

We have completed our study of this application which became conditionally effective on May 23, 1962 and it is effective. The application became effective prior to the enactment of the Drug Amendments of 1962 but in accordance therewith is deemed to be an approved application under the Federal Food, Drug, and Cosmetic Act. Our letter of May 23, 1962

detailed the conditions relating to the approval of this application.

Sincerely yours,

s/ EPM

EMMETT P. MADIGAN, M.D.
Medical Officer
Division of New Drugs
Bureau of Medicine

cc: SL(w/dup matl)
DND ILLEGIBLE
BM
FMcKinlay/bs
2/7/63
Eff. Orig.

LETTERHEAD —

DEPARTMENT OF HEALTH & HUMAN SERVICES

OBERO J
213 PRES RAMIRE ST
HATO REY, PR 00918

10/05/92
In reply refer to:
92035490

Dear Requester:

Your request (copy enclosed) for records has been received by the Food and Drug Administration, Freedom of Information Staff, and we will respond as soon as possible. Pursuant to Departmental regulations, applicable charges will be assessed.

All communications concerning this request should be identified with the reference number above and addressed as follows:

Food and Drug Administration
Freedom of Information Staff, HFI-35
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

s/ SHERA S. BEHRAM

SHERA S. BEHRAM
Information Technician

(302) 443-6310
Enclosures:
as indicated
(301) 443-4748
4747

Joseph Oteco
213 Pres Ramirez St
Hao rey PR 00918

The attached document shows that that the GE CT 9800 has been cleared for commercial distribution by FDA. FDA does not approve devices — it only approves their commercial distribution.

If you wish a duplicate of the exact letter sent to GE authorizing commercial distribution you must resubmit your FOI request to FDA. FDA FOI did not interpret your request to be that specific. My office does not have these clearance letters. I believe it would be some time before a copy of the letter would be issued.

Arthur Kohler/Consumer Safety Officer
HFZ 220 1-800-638-2041

Alt-Z FOR HELP° VT102 ° FDX ° 9600 N81 °
LOG CLOSED ° PRINT OFF ° ON LINE

★ ★

Doc No: K841997	Cont Conf: 9	Status: c
Login Date:	Letter Date:	Due Date:
84/05/16	/ /	84/08/17

★ ★

MANUFACTURER INFORMATION

Mfgname: GENERAL ELECTRIC CO.
Contact: Shortname: GENEELEC
Street1: Estab No: MISSING
Street2:
City: State: Zip:
Phone: Country:

★ ★

Product Name: CT 9800
Rev Panel: RA Pan/Prod Code(s): RA/JAK / / / /
Branch: ★
Decision:SE Rqst Date: / / Due Date: / / Login Date: / /

Date: 84/09/04	Date: / /	Date: / /	Date: / /
510k Summary:	Date: / /	Date; / /	Date; / /
510k Statement:	Date: / /	Date: / /	Date: / /
Class 3 Summary:	Date: / /	Date: / /	Date: / /
PMS:	Date: / /	Date: / /	Date: / /

Comments:

★ ★

K841997

LETTERHEAD—

DEPARTMENT OF HEALTH & HUMAN SERVICES

May 17, 1984

D.C. Number: See Attached Sheet
Received: 5-16-84
Product:

General Electric Company
ATTN: James M. Howard, II
P.O. Box 414
Milwaukee, WI 53201

The Premarket Notification you have submitted as required under Section 510(k) of the Federal Food, Drug and Cosmetic Act for the above referenced device has been received and assigned a unique document control number (D.C. Number above). Please cite this D.C. Number in any future correspondence that relates to this submission.

We will notify you when the processing of this submission has been completed or if any additional information is required. You are required to wait ninety (90) days after the received date shown above or until receipt of a "substantially equivalent" letter before placing the product into commercial distribution. I would suggest that you contact us if you have not been notified in writing at the end of this ninety (90) day period before you begin marketing your device. Questions concerning this submission should be sent to:

Food and Drug Administration
National Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
8757 Georgia Avenue
Silver Spring, Maryland 20910

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at their toll-free number (800) 638-2041 or me at (301) 427-7230.

Sincerely yours,

s/ ROBERT I. CHISSLER

ROBERT I. CHISSLER
Premarket Notification Coordinator
Office of Device Evaluation
National Center for Devices and
Radiological Health

LETTERHEAD —

DEPARTMENT OF HEALTH & HUMAN SERVICES

Sep 4 1984

Mr. James M. Howard, II
Manager, Regulatory Engineering
Medical Systems Group
General Electric Company
P.O. Box 414
Milwaukee, Wisconsin 53201

Re: K841997
CT 9800
Dated: May 9, 1984
Received:
May 16, 1984

Dear Mr. Howard:

We have reviewed your Section 510(k) notification of intent to market the above device and we have determined the device to be substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market your device subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (Act) until such time as your device has been classified under Section 513. At that time, if your device is classified into either class II (Performance Standards) or class III (Premarket Approval), it would be subject to additional controls. Please note: This action does not affect any obligation you might have under the Radiation Control for Health and Safety Act of 1968, or other Federal Laws or regulations.

General controls presently include regulations on annual registration, listing of devices, good manufacturing practice, labeling, and the misbranding and adulteration provisions of the Act. In the future, the scope of general controls may be broadened to include additional regulations.

All regulations and information on meetings of the device advisory committees, their recommendations, and the final

decisions of the Food and Drug Administration (FDA) will be published in the *Federal Register*. We suggest you subscribe to this publication so you can convey your views to FDA if you desire and be notified of any additional requirements imposed on your device. Subscriptions may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Such information also may be reviewed in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857.

This letter does not in any way denote official FDA approval of your device or its labeling. Any representation that creates an impression of official approval of this device because of compliance with the premarket notification regulations is misleading and constitutes misbranding. If you desire advice on the labeling for your device or other information on your responsibilities under the Act, please contact the Office of Compliance, Division of Compliance Operations (HFZ-320), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

Sincerely yours,

s/ ROBERT G. BRITAIN

ROBERT G. BRITAIN
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

MICROFILMED ILLEGIBLE
AVAILABLE ILLEGIBLE

RADIOLOGICAL DEVICES BRANCH — SIDE EVALUATION FORM

PK 841997

Company Name: GENERAL ELECTRIC COMPANY

Device Name: CT 9800 Dual Energy

		Yes	No
1.	Life-supporting or life sustaining?	____	____
2.	Implant (short-term or long-term?)	____	____
3.	Is sterility involved?	____	____
4.	If appropriate: provides comparative lab data:	_____	
	provides a summary of animal testing:	_____	
	provides a summary of clinical testing:	_____	

5. I believe this is equivalent to device(s):
   Computer Tomography X-ray System (Class Name)
   Classification should be based on:
   Procode: 90 JAK CFR #:892.1750
   Class: II Proposed ✓ Final ____
   Is this an accessory to the above device?
   Yes ____ No ✓
   Similar preenactment device(s):
   CT 8800 and CT 9800, G.E.
   (Device name, Manufacturer)
6. I believe this is not equivalent to any preenactment device. ____
7. Differs from preenactment devices how?
   This device has the capability to change the x-ray beam filter for additional shaping of the x-ray spectra. It also has additional analysis software.

8. I believe that (clinical, animal, lab) testing is required before a determination can be made. _____
9. Comment: The info submitted on 8/30/84 re comparative dose rates shows no significant increase in dose to patient.

s/ ADRIANNE GALDI
(sign & date)

Returned for
comparative dose
path.
09/06/84

APPENDIX I

SPONTANEOUS REPORTING SYSTEM
DIVISION OF DRUG AND BIOLOGICAL PRODUCT EXPERIENCE
Brief Description with Caveats of the System

Background:

The Spontaneous Reporting System (SRS) of DDBPE is a computerized data base of adverse reactions reported by health professionals. The present data base contains approximately 200,000 reports collected since 1969. The system contains only adverse reactions detected and reported after marketing of the drug. The primary purpose for maintaining the data base is to serve as an early warning system or signaling system for adverse drug reactions not detected during premarket testing.

The SRS depends on a health professional's detecting a new clinical event, attributing the appearance of the clinical event to the administration of a drug and reporting that clinical event to a drug company or to the FDA.

The health professional may choose to report the adverse reaction to a drug firm, who must, by law, report to the FDA. Eighty percent of DDBPE's reports are received from drug manufacturers. DDBPE receives the remaining twenty percent directly from the reporter.

Data from all reports are entered into the DDBPE computer and the reports are stored on microfilm.

Caveats:

There are important things to remember when reviewing or analyzing data from the Spontaneous Reporting System.

1. For any given report, there is no certainty that the drug caused the reaction. This is because physicians are encouraged to report suspected reactions. In many instances, the event may have been related to the underlying disease for which the drug was given and not the drug itself.
2. The accumulated case reports can not be inferred to reflect national incidences or estimates of drug risk.
3. Rates and/or frequencies generated from these data must be carefully interpreted as reporting rates and not occurrence rates. True incidence rates cannot be determined from this database.
4. Since reporting is voluntary it depends on many factors. This leads to reporting artifacts which must be kept in mind by anyone reviewing these data. Therefore comparisons of drugs for their relative safety should not be done without a complete understanding of the following and their impact on the comparisons.
   a. Length of time the drug has been marketed
   b. Size of manufacturer's sales force
   c. Training of manufacturer's sales force for collecting adverse reactions
   d. Market share of the drug
   e. Articles in the medical literature
   f. Special promotions and advertising
   g. Special studies or marketing studies
   h. Manufacturer reporting practices
   i. Articles in the lay press
   j. Regulatory action
5. All drugs entered into the computer in association with a case report are given equal status as to their association with the reported reactions, even though the reporter may have suspected a particular drug. Separating the drug reported as suspect in causing the reaction from the other concomitant drugs must be done by a special computer search.

6. Duplicate reports exist in the file. This must be kept in mind especially when generating and reviewing summary counts. There are two reasons for duplication.
   a. FDA was unable to determine that a report was previously submitted and computerized.
   b. A follow-up report was received, identified and entered as a separate case report. This is potentially solvable by examining the accession number on a detailed computer printout. The last digit of the accession number is "1" for initial reports and a number greater than 1 which represents a follow-up report.

System Problems

Three additional system problems should be kept in mind.

1. *Terms and Drugs versus Reports.*
   In describing a report up to four adverse reaction terms per report and up to five drugs may be entered into the computer. Therefore there may exist up to 20 drug reaction associations per case. All terms will be printed out.

   Term Example:

   A patient was given Drug A and experienced abnormal liver function, gastrointestinal hemorrhage, a bullous rash and increased heart rate. This one report would generate four reaction terms:

Drug	*Reaction Dictionary Term*
A	Liver Function Abnorm
	Hem GI
	Rash Vesic Bull
	Tachycardia

Drug Example:

A patient experienced perforated ulcer while on drug A, B, C, D and E. This report will generate five drug-reaction associations.

Drug	*Reaction Dictionary Term*
A	Ulcer Per
B	
C	
D	
E	

2. *Computer System.*

The present computer system will not allow much of the computer analysis we would like. Much of the data analysis remains a labor intensive effort.

Mark IV programs produce summary counts by looping through segments and counting occurrences in a unique manner. Care should be taken to thoroughly understand the generation of the counts and to verify the accuracy of any programs generating summary counts.

3. *Regulations.*

The regulations mandate reporting of an unlabeled serious adverse reaction within 15 days. It is frequently difficult to obtain follow-up information within that time period, which leads to incomplete reports. Sometimes this follow-up data is not obtainable and the report remains computerized but unevaluable.

USE OF THE ADVERSE DRUG REACTION COMPUTER PRINTOUTS

REPORTS FROM THE VOLUNTARY REPORTING SYSTEM OF THE DIVISION OF DRUG AND BIOLOGICAL PRODUCT EXPERIENCE, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MARYLAND 20857

This report consists of two parts, the first of which is a list of the drugs and associated reactions with counts of the total reported occurrences of such reactions. The second part is a detailed breakdown of each case and includes parameters such as reaction, daily dose, dosage form, route of administration, duration of therapy, age, sex, and number of concomitant drugs in therapy.

PARAMETERS ON DETAIL REPORT

ACCESSION NUMBER

This is a number assigned by the Division of Drug and Biological Product Experience. The first 2 digits represent the year the FDA received the report. The second 2 digits represent the month.

REACTION

This system represents the suspected reaction(s) indexed from FDA-s Coding Symbols for a Thesaurus of Standard Adverse Reaction Terms (COSTART).

UNITS*

This modifies the daily dose.

*Most frequently used terms.

GM - gram
MG - milligram
TB - tablets
GR - grain
SUP - suppositories
MU - micrograms
ME - milliequivalents
IU - international units
ML - milliliters

DOSAGE FORM*

SUP - suppositories
TAB - tablets
SYR - syrup
SRS - sustained release capsules
INJ - injection
SUS - suspension

ROUTE ADM*

Route of administration.

PO - oral
IV - intravenously
RTL - rectal
OPH - ophthalmic
TOP - topical
INH - inhalation

AGE

This represents the approximate age of the patient in years at the time of the reaction. An unknown age is given as UNK.

DURATION THERP

Duration of therapy in days.

SEX

F = female
M = male
Blank = unknown

OTHER DRUGS

This parameter indicates the number of other drugs reported that were administered concomitantly with the

*Most frequently used terms.

requested drug. An eight (8) in the first digit of this number indicates that there is a possibility that drugs other than those reported were administered.

PATIENT OUTCOME

This indicates the state of the patient's reaction at the time of the report. If blank, this was not reported.

REC = recovered SUT = still under treatment
A/S = alive with sequelae

Fatal is the other possibility.

CASE NUMBER

This ia a unique number assigned to reports received by the Division of Drug and Biological Product Experience as they are computerized. It represents the number the report is filed under on microfilm.

MESSAGE

This parameter provides other verbal information not included in the other parameters which is helpful to the understanding of the report.

This printout contains both initial reports and sometimes follow-up reports to a given case. To distinguish these, the key is in the accession number. Initial reports have a last digit of "1." Follow-up reports (for the same case) will have exactly the same accession number, except the last digit which will be a "2" or greater. (The case number will be different but it is still the same case if the accession numbers correlate in this way.)

Caution concerning the "total reactions" count on the first part of the printout:

This counts both initial and follow-up reports to the same case separately. Therefore, if a "2" appears, it may still be only *one* case in reality. This is necessary in order to have the follow-ups appear on the second part of the printout.

9/12/85

08/13/87

FDA SPONTANEOUS REPORTING SYSTEM

CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Agitation	7
Domestic	Allerg React	121
Domestic	Amblyopia	9
Domestic	Amnesia	12
Domestic	Anaphyl	86
Domestic	Aneurysm Intracran	1
Domestic	Angina Pectoris	1
Domestic	Angioedema	7
Domestic	Anuria	4
Domestic	Anxiety	6
Domestic	Aphasia	19
Domestic	Apnea	26
Domestic	Arachnoiditis	1
Domestic	Arrhythmia	3
Domestic	Arteriospasm	7
Domestic	Arthralgia	2
Domestic	Asthenia	14
Domestic	Asthma	63
Domestic	Ataxia	3
Domestic	Av Block SD	1
Domestic	Babinski Sign Pos	1
Domestic	Bilirubinem	1
Domestic	Blind	22
Domestic	Bradycardia	8

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Brain Synd Acute	4
Domestic	Cellulitis	1
Domestic	Cerebrovasc Accid	17
Domestic	Chills	121
Domestic	Chills Fever	22
Domestic	Chrondrodyst	22
Domestic	Coagul Dis	7
Domestic	Coma	37
Domestic	Confus	48
Domestic	Conjunctivitis	34
Domestic	Convuls	50
Domestic	Convuls Grand Mal	9
Domestic	Coordinat Abnorm	1
Domestic	Cough Inc	31
Domestic	Creatine Pk Inc	1
Domestic	Cyanosis	14
Domestic	Death	17
Domestic	Delirium	1
Domestic	Delusions	1
Domestic	Diplopia	4
Domestic	Dizziness	29
Domestic	Dry Mouth	2
Domestic	Dysarthria	1
Domestic	Dysphagia	25
Domestic	Dyspnea	163
Domestic	Ecg Abnorm	1
Domestic	Edema	8
Domestic	Edema Brain	3
Domestic	Edema Conjunct	1
Domestic	Edema Face	108
Domestic	Edema General	4
Domestic	Edema Inject Site	14

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Edema Larynx	33
Domestic	Edema Lung	7
Domestic	Edema Periph	9
Domestic	Edema Tongue	4
Domestic	Emb Arm	1
Domestic	Emb Coronary	1
Domestic	Emb Pulm	2
Domestic	Encephalitis	1
Domestic	Erythema Mult	1
Domestic	Esr Inc	2
Domestic	Fever	28
Domestic	Fibrillat Atr	2
Domestic	Fibrillat Vent	2
Domestic	Fibrinogen Dec	1
Domestic	GI Dis	1
Domestic	Hallucin	3
Domestic	Headache	38
Domestic	Heart Arrest	34
Domestic	Hem	1
Domestic	Hem Cerebr	5
Domestic	Hem Inject Site	2
Domestic	Hem Subarachnoid	1
Domestic	Hematuria	1
Domestic	Hemiplegia	32
Domestic	Hostility	5
Domestic	Hyperkinesia	1
Domestic	Hypertens	29
Domestic	Hypertonia	2
Domestic	Hyperventil	2
Domestic	Hypesthesia	6
Domestic	Hypotens	116
Domestic	Hypotonia	2

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Hypoventil	6
Domestic	Hypoxia	2
Domestic	Hysn Inject Site	14
Domestic	Hysteria	3
Domestic	Incontin Urin	1
Domestic	Infarct Cerebr	2
Domestic	Infarct Myocard	3
Domestic	Infect	3
Domestic	Infect Urin Tract	1
Domestic	Inflam Inject Site	5
Domestic	Inject Site React	19
Domestic	Ischemia Cerebr	8
Domestic	Ischemia Myocard	1
Domestic	Jaundice	3
Domestic	Joint Dis	1
Domestic	Keratoconjunctivitis	1
Domestic	Kidney Fail	5
Domestic	Kidney Fail Acute	6
Domestic	Lacrimation Dis	2
Domestic	Laryngismus	16
Domestic	Laryngitis	5
Domestic	Leukopenia	1
Domestic	Liver Damage	1
Domestic	Liver Func Abnorm	2
Domestic	Lung Dis	8
Domestic	Malaise	4
Domestic	Meningism	1
Domestic	Myalgia	1
Domestic	Myasthenia	4
Domestic	Myelitis	1
Domestic	Myocarditis	1
Domestic	Nausea	101

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Nausea Vomit	115
Domestic	Nausea Vomit Diar	2
Domestic	Neck Rigid	1
Domestic	Necro	1
Domestic	Necro Inject Site	4
Domestic	Nervousness	7
Domestic	Neuropathy	4
Domestic	No Drug Effect	7
Domestic	Nystagmus	4
Domestic	Occlus	1
Domestic	Occlus Carotid	2
Domestic	Oculogyric Crisis	1
Domestic	Osteomyelitis	2
Domestic	Pain	17
Domestic	Pain Abdo	21
Domestic	Pain Back	12
Domestic	Pain Chest	45
Domestic	Pain Chest Substern	2
Domestic	Pain Ear	1
Domestic	Pain Inject Site	24
Domestic	Pain Neck	3
Domestic	Pallor	5
Domestic	Palpitat	3
Domestic	Pancreas Dis	1
Domestic	Paralysis	11
Domestic	Paraplegia	4
Domestic	Paresth Circumoral	4
Domestic	Paresthesia	18
Domestic	Parotid Enlarge	1
Domestic	Person Dis	3
Domestic	Petechia	1
Domestic	Pharyngitis	55

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Phleb	44
Domestic	Pneumonia	1
Domestic	Pneumonia Aspir	1
Domestic	Pruritus	148
Domestic	Psychosis	4
Domestic	Purpura	3
Domestic	Quadriplegia	5
Domestic	Rash	93
Domestic	Rash Mac Pap	3
Domestic	Rash Vesic Bull	2
Domestic	React Aggrav	3
Domestic	React Uneval	1
Domestic	Reflexes Inc	1
Domestic	Respirat Dis	8
Domestic	Rhinitis	111
Domestic	Salpingitis	1
Domestic	Sepsis	4
Domestic	Shock	39
Domestic	Somnolence	16
Domestic	Speech Dis	16
Domestic	Sputum Inc	1
Domestic	Stridor	3
Domestic	Stupor	9
Domestic	Sweat	16
Domestic	Syncope	17
Domestic	Tachycardia	21
Domestic	Tachycardia Vent	2
Domestic	Taste Pervers	4
Domestic	Thinking Abnorm	3
Domestic	Throm Carotid	1
Domestic	Thrombophleb	6
Domestic	Tinnitus	1

CONRAY

Report Source	*Costart*	*Total Occurrences*
Domestic	Tremor	17
Domestic	Twitch	4
Domestic	Uremia	1
Domestic	Urin Retent	1
Domestic	Urticaria	677
Domestic	Vasc Dis Periph	2
Domestic	Vasodilat	90
Domestic	Vertigo	2
Domestic	Vision Abnorm	12
Domestic	Visual Field Defect	6
Domestic	Voice Alterat	8
Domestic	Vomit	72
Domestic	Yawn	1
Domestic		3676
Foreign	Allerg React	8
Foreign	Amnesia	1
Foreign	Anaphyl	4
Foreign	Apnea	1
Foreign	Arrhythmia	1
Foreign	Asthma	1
Foreign	Blind	1
Foreign	Bradycardia	3
Foreign	Cerebrovasc Accid	1
Foreign	Chills	1
Foreign	Coagul Dis	1
Foreign	Confus	2
Foreign	Conjunctivitis	1
Foreign	Convuls	1
Foreign	Convuls Grand Mal	1
Foreign	Cough Inc	4
Foreign	Cyanosis	1
Foreign	Death	4

CONRAY

Report Source	*Costart*	*Total Occurrences*
Foreign	Dizziness	1
Foreign	Dyspnea	8
Foreign	Edema	1
Foreign	Edema Face	4
Foreign	Eosinophilia	1
Foreign	Extrasystoles Vent	1
Foreign	Fever	1
Foreign	Hallucin	1
Foreign	Headache	3
Foreign	Heart Arrest	1
Foreign	Hemiplegia	1
Foreign	Hyperventil	2
Foreign	Hypesthesia	2
Foreign	Hypophosphatem	1
Foreign	Hypotens	6
Foreign	Hypoxia	1
Foreign	Infarct Myocard	1
Foreign	Kidney Fail	1
Foreign	Laryngitis	1
Foreign	Migraine	1
Foreign	Nausea	8
Foreign	Nausea Vomit	16
Foreign	No Drug Effect	1
Foreign	Pain Abdo	2
Foreign	Pain Chest	6
Foreign	Pancreatitis	1
Foreign	Paresthesia	1
Foreign	Pharyngitis	3
Foreign	Pruritus	5
Foreign	Rash	5
Foreign	Retinal Vasc Dis	1
Foreign	Rhinitis	10

CONRAY

Report Source	*Costart*	*Total Occurrences*
Foreign	Shock	1
Foreign	Sweat	2
Foreign	Syncope	2
Foreign	Urticaria	48
Foreign	Vasodilat	17
Foreign	Voice Alterat	1
Foreign	Vomit	1
Foreign		207
Tot Drug Count		3883

CONRAY SPECIAL STUDIES

Report Source	*Costart*	*Total Occurrences*
Domestic	Anaphyl	1
Domestic		1
Tot Drug Count		1

CONRAY 43

Report Source	*Costart*	*Total Occurrences*
Domestic	Agitation	2
Domestic	Anaphyl	1
Domestic	Angioedema	1
Domestic	Anxiety	3
Domestic	Apnea	4
Domestic	Arthralgia	1
Domestic	Asthenia	2
Domestic	Asthma	3
Domestic	Chills	14
Domestic	Chills Fever	2

CONRAY 43

Report Source	*Costart*	*Total Occurrences*
Domestic	Coma	2
Domestic	Confus	2
Domestic	Conjunctivitis	2
Domestic	Convuls	2
Domestic	Convuls Grand Mal	3
Domestic	Cough Inc	7
Domestic	Cyanosis	2
Domestic	Dizziness	3
Domestic	Dysphagia	1
Domestic	Dyspnea	14
Domestic	Edema Face	15
Domestic	Edema Larynx	3
Domestic	Fever	2
Domestic	Gangrene	1
Domestic	Headache	1
Domestic	Heart Arrest	1
Domestic	Heart Fail Right	2
Domestic	Hematemesis	1
Domestic	Hemiplegia	1
Domestic	Hypertens	3
Domestic	Hyperventil	1
Domestic	Hypokalem	1
Domestic	Hypotens	6
Domestic	Hypotens Post	1
Domestic	Hysn Inject Site	1
Domestic	Incontin Fecal	1
Domestic	Incontin Urin	1
Domestic	Infarct Cerebr	1
Domestic	Inject Site React	1
Domestic	Ischemia Cerebr	2
Domestic	Laryngismus	1
Domestic	Leukocytosis	1

CONRAY 43

Report Source	*Costart*	*Total Occurrences*
Domestic	Nausea	7
Domestic	Nausea Vomit	8
Domestic	Nausea Vomit Diar	1
Domestic	Pain	1
Domestic	Pain Abdo	1
Domestic	Pain Chest	2
Domestic	Pallor	3
Domestic	Palpitat	1
Domestic	Paresthesia	2
Domestic	Pharyngitis	18
Domestic	Pruritus	16
Domestic	Rash	10
Domestic	Rash Vesic Bull	1
Domestic	Respirat Dis	1
Domestic	Rhinitis	5
Domestic	Saliva Inc	1
Domestic	Shock	2
Domestic	Skin Discolor	2
Domestic	Somnolence	3
Domestic	Stupor	1
Domestic	Sweat	5
Domestic	Syncope	1
Domestic	Tachycardia	1
Domestic	Tremor	5
Domestic	Urticaria	76
Domestic	Vasodilat	4
Domestic	Vision Abnorm	2
Domestic		299
Tot Drug Count		299

CONRAY-325

Report Source	*Costart*	*Total Occurrences*
Domestic	Arrhythmia	2
Domestic	Bradycardia	1
Domestic	Chills	1
Domestic	Chills Fever	1
Domestic	Coagul Dis	1
Domestic	Cough Inc	2
Domestic	Cyanosis	1
Domestic	Dyspnea	4
Domestic	Edema Face	1
Domestic	Edema Inject Site	1
Domestic	Edema Larynx	1
Domestic	Hypertens	1
Domestic	Hypotens	4
Domestic	Nausea Vomit	1
Domestic	Necro Kidney Cortex	1
Domestic	Pain	5
Domestic	Pain Abdo	1
Domestic	Pain Chest	4
Domestic	Pain Inject Site	1
Domestic	Paresthesia	2
Domestic	Rash	1
Domestic	Sepsis	1
Domestic	Shock	1
Domestic	Stridor	1
Domestic	Tachycardia	2
Domestic	Tremor	2
Domestic	Urticaria	8
Domestic	Venospasm	3
Domestic	Vomit	1
Domestic		56
Foreign	Coma	1
Foreign		1
Tot Drug Count		57

CONRAY-400

Report Source	*Costart*	*Total Occurrences*
Domestic	Allerg React	2
Domestic	Amblyopia	1
Domestic	Amnesia	1
Domestic	Anaphyl	45
Domestic	Angina Pectoris	2
Domestic	Angioedema	2
Domestic	Aphasia	1
Domestic	Apnea	13
Domestic	Arrhythmia	1
Domestic	Asthenia	2
Domestic	Asthma	28
Domestic	Blind	1
Domestic	Bradycardia	4
Domestic	Cardiovasc Dis	1
Domestic	Cellulitis	1
Domestic	Cerebrovasc Accid	1
Domestic	Chills	32
Domestic	Chills Fever	6
Domestic	Coagul Dis	1
Domestic	Coma	6
Domestic	Confus	4
Domestic	Conjunctivitis	5
Domestic	Convuls	8
Domestic	Convuls Grand Mal	2
Domestic	Cough Inc	10
Domestic	Cyanosis	9
Domestic	Death	7
Domestic	Dizziness	6
Domestic	Dysphagia	3
Domestic	Dyspnea	58
Domestic	Ecchymosis	1
Domestic	Edema	7

CONRAY-400

Report Source	*Costart*	*Total Occurrences*
Domestic	Edema Face	48
Domestic	Edema Inject Site	7
Domestic	Edema Larynx	16
Domestic	Edema Lung	2
Domestic	Emb Pulm	1
Domestic	Extrasystoles Bigem	1
Domestic	Eye Dis	1
Domestic	Fever	8
Domestic	Fibrillat Vent	3
Domestic	Glossitis	1
Domestic	Headache	8
Domestic	Heart Arrest	29
Domestic	Heart Block	1
Domestic	Heart Fail	2
Domestic	Hem GI	1
Domestic	Hem Inject Site	1
Domestic	Hypalgesia	1
Domestic	Hypertens	5
Domestic	Hypertonia	1
Domestic	Hypokalem	1
Domestic	Hypotens	56
Domestic	Hypoventil	3
Domestic	Hypoxia	1
Domestic	Hysn Inject Site	6
Domestic	Infarct Myocard	9
Domestic	Infect	1
Domestic	Inflam Inject Site	12
Domestic	Inject Site React	1
Domestic	Ischemia Myocard	1
Domestic	Laryngismus	11
Domestic	Lymphangitis	4
Domestic	Malaise	2

CONRAY-400

Report Source	*Costart*	*Total Occurrences*
Domestic	Nausea	32
Domestic	Nausea Vomit	31
Domestic	Necro Inject Site	1
Domestic	Neuralgia	1
Domestic	No Drug Effect	2
Domestic	Occlus Coronary	2
Domestic	Pain	36
Domestic	Pain Abdo	7
Domestic	Pain Back	2
Domestic	Pain Chest	11
Domestic	Pain Inject Site	47
Domestic	Pallor	1
Domestic	Paralysis	2
Domestic	Paresthesia	16
Domestic	Pharyngitis	1
Domestic	Phleb	31
Domestic	Pruritus	14
Domestic	Rash	34
Domestic	Rash Mac Pap	3
Domestic	Rhinitis	10
Domestic	Shock	29
Domestic	Skin Dis	1
Domestic	Skin Discolor	1
Domestic	Speech Dis	1
Domestic	Sweat	11
Domestic	Syncope	7
Domestic	Tachycardia	6
Domestic	Tachycardia Vent	1
Domestic	Throm	1
Domestic	Thrombophleb	18
Domestic	Tremor	6
Domestic	Urticaria	158

CONRAY-400

Report Source	*Costart*	*Total Occurrences*
Domestic	Vasculitis	1
Domestic	Vasodilat	11
Domestic	Vasospasm	1
Domestic	Venospasm	3
Domestic	Voice Alterat	1
Domestic	Vomit	8
Domestic		1065
Foreign	Amnesia	1
Foreign	Anaphyl	1
Foreign	Angioedema	1
Foreign	Apnea	1
Foreign	Asthma	3
Foreign	Bradycardia	1
Foreign	Confus	1
Foreign	Convuls	1
Foreign	Dizziness	3
Foreign	Dysphagia	1
Foreign	Dyspnea	2
Foreign	Dystonia	1
Foreign	Edema Face	1
Foreign	Edema Inject Site	1
Foreign	Edema Periph	1
Foreign	Headache	1
Foreign	Heart Arrest	4
Foreign	Hypertens	1
Foreign	Hypotens	6
Foreign	Hypoventil	1
Foreign	Nausea	8
Foreign	Nausea Vomit	4
Foreign	No Drug Effect	1
Foreign	Pain	4
Foreign	Pain Abdo	2

CONRAY-400

Report Source	*Costart*	*Total Occurrences*
Foreign	Pain Inject Site	1
Foreign	Paralysis Flaccid	1
Foreign	Pruritus	1
Foreign	Rash	1
Foreign	Rhinitis	2
Foreign	Shock	7
Foreign	Somnolence	1
Foreign	Syncope	1
Foreign	Tachycardia	2
Foreign	Thrombophleb	1
Foreign	Urticaria	3
Foreign		73
Tot Drug Count		1138

Report Source	*Costart*	*Total Occurrences*
Grand Count		5378

***** FT03 TYPE 0 END OF REPORT.

***** ED02 TYPE 0 REQUEST-SELECTD2
REPORT-2 REQUESTOR ID —

DRUG EXPERIENCE REPORT

RETURN TO: MALLINCKRODT, INC.
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, Missouri 63134
Attn: Medical Director

I. REACTION INFORMATION

1. Patients ID/Initials *(in Confidence)*

R.O.L.

2. Age in Years

34

3. Sex

Male

4.-6. Reaction Onset

February 21, 1986

7. Describe Reaction(s) *(Underline single most important clinical event or reaction term)*

After 50cc of Conray 60% developed a generalized seizure that last for few seconds, after that patient went into cardio-respiratory arrest. Was declared dead after unsuccessful attempt of resucitation. Patient had several skin lesions diagnosed as mastocytosis by biopsy.

8.-12. Check all appropriate to reaction

- ☒ Died due to reaction
- ☐ Treated with Rx drug
- ☐ Resulted in, or prolonged, inpatient hospitalization
- ☐ Resulted in severe or permanent disability
- ☐ None of the above

13. Relevant Tests/Laboratory Data

II. SUSPECT DRUG(S) INFORMATION

14. Suspect Drug(s) *(Give manufacturer and lot no. for vaccines/biologics)*

Iothalamate meglumine injection.
USP 60% Conray – Lot No. 162 B – Exp. Date 9/88

15. Daily Dose

16. Route of Administration

I.V.

17. Indication(s) For Use

18. Therapy Dates *(From/To)*

19. Therapy Duration

8 minutes.

20. Did reaction abate after stopping drug?

No

21. Did reaction reappear after reintroduction?

III. CONCOMITANT DRUGS AND HISTORY

22. Concomitant Drugs and Dates of Administration *(Exclude those used to treat reaction)*

23. Other Relevant History *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

R/O Early viral meningitis or encephalitis. No previous allergies were informed.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. Name and Address of Manufacturer *(Include Zip Code)*

24a. IND/NDA No. For Suspect Drug

24b. Manufacturer Control No.

24c. Date Received By Manufacturer

24d. Report Source *(Check one)*

☐ Foreign ☐ Study ☐ Literature
☐ Health Professional ☐ Consumer

25. 15 Day Report

25a. Report Type

V. INITIAL REPORTER *(In confidence)*

26.-26a. Name and Address of Reporter *(Include Zip Code)*

Jose N. Lazaga, M.D.
Central CT
P.O. Box 3670
Hato Rey, P.R. 00919

26b. Telephone No. *(Include area code)*

(809) 758-9196

26c. Have You Also Reported This Reacton to the Manufacturer?

Yes

26d. Are You a Health Professional?

Yes

APPENDIX J

FEDERAL REGISTER, VOL. 42, NO. 161 — FRIDAY, AUGUST 19, 1977

41917

2. *Labelling conditions.* (a) The labels bears the statement, "Caution: Federal law prohibits dispensing without prescription."

(b) Approval of an abbreviated new drug application (21 CFR 314.1(f)), must be obtained prior to marketing such products. The applications shall contain full information with respect to items 6 (components), 7 (composition) and 3 (methods, facilities, and controls) of new drug application form FD-356H (31 CFR 314.1(c)). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70).

Dated: August 8, 1977.

CARL M. LEVENTHAL
Acting Director Bureau of Drugs

[FR Doc. 77-23652; Filed 8-18-77; 8:45 am]